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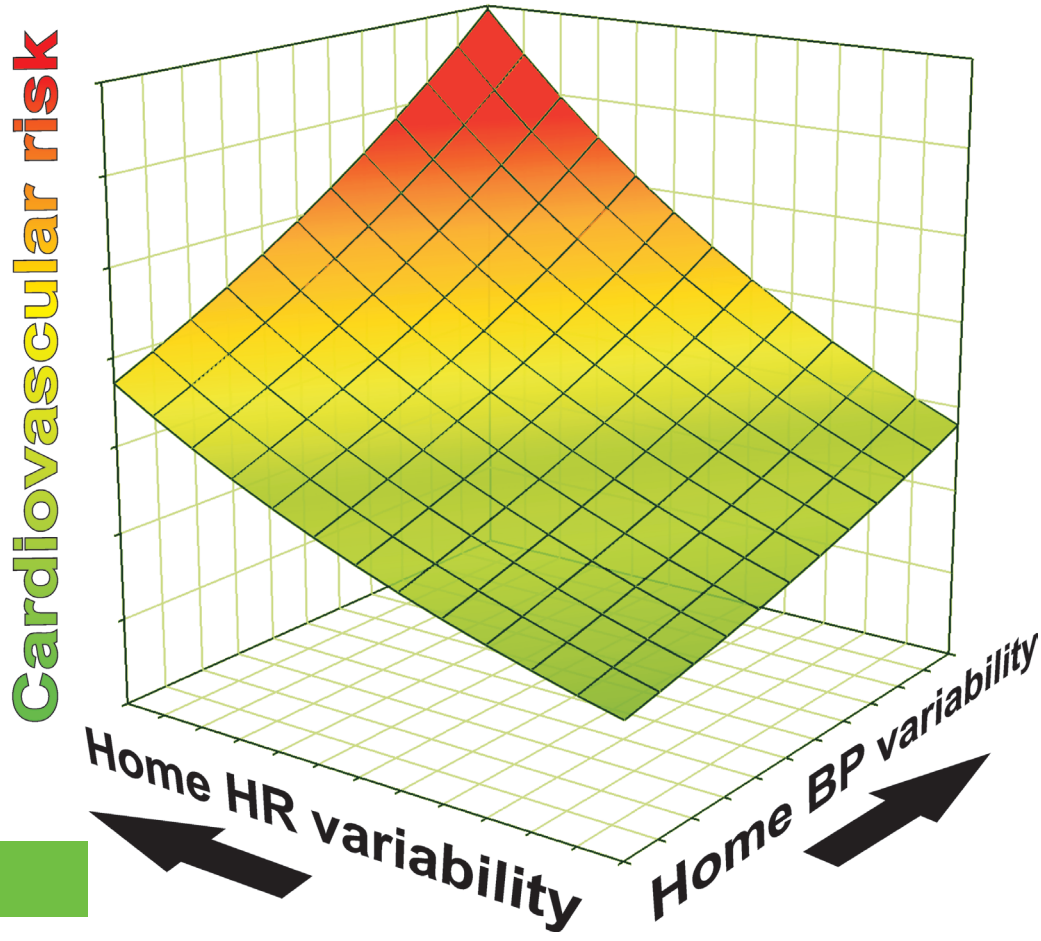
RESEARCH

Jouni Johansson

Optimal Schedule for Home Blood Pressure Measurements and Clinical Significance of the Variability in Home-Measured Blood Pressure and Heart Rate



RESEARCH NR 66

Jouni Johansson

Optimal schedule for home blood pressure measurements and clinical significance of the variability in home-measured blood pressure and heart rate

ACADEMIC DISSERTATION

To be presented with the permission of the Faculty of Medicine, University of Turku, for public examination in the auditorium of the Petrea Rehabilitation Centre, Turku on October 14th, 2011, at 12 noon.

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To my family

Abstract

Jouni Johansson. Optimal schedule for home blood pressure measurements and clinical significance of the variability in home-measured blood pressure and heart rate. National Institute for Health and Welfare (THL). Research 66, 178 pages. Turku, Finland 2011.
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Hypertension is still a great burden in worldwide healthcare as it is one of the major causes of death globally. Accurate knowledge of the true blood pressure (BP) level is vital for optimal prevention and treatment of hypertension. Home BP monitoring has become popular due to cheap electronic devices. This thesis was set out to provide insight into building an optimal measurement schedule for home BP monitoring, and to evaluate how to increase the prognostic value of home monitoring by using variability parameters of home BP and heart rate measured over several days.

The material was based on two studies. The Finn-home study consisted of a representative sample of the Finnish adult population (2106 individuals aged 41-74 years). Study subjects underwent a clinical interview, attended a health examination and measurements of home BP and home heart rate over 7 days. The Finn-home study included follow-up data of cardiovascular events. The second study population consisted of 228 study subjects aged 34-64 years living in southwestern Finland who were randomly drawn from the population register, and of 236 newly diagnosed, yet untreated, moderately to severely hypertensive men and women, aged 35-54 years from southwestern Finland. Study subjects underwent a thorough clinical examination including echocardiography, measurements of microalbuminuria, ambulatory BP and 7-day self-measured home BP.

Based on the associations of ambulatory BP, target organ damage and risk of future cardiovascular events with home BP, the measurement accuracy of home BP increased with cumulative number of measurements. Most of the increase occurred during the first 3 days.

In contrast to what the European guidelines (2008) suggest, measurements performed during the first day should not be discarded, as

it makes the measurement schedule more complex for the patient and the treating physician. The variability of home BP and heart rate predicted independently future cardiovascular events. Male gender, excessive use of alcohol, use of antihypertensive medication, past history of cardiovascular disease and sleep apnea were found to be independent determinants of elevated morning home BP in relation to evening BP. Old age, diabetes, history of cardiovascular disease and excessive use of alcohol were independent determinants of increased home BP variability. Young age and moderate use of alcohol were independently associated with increased home heart rate variability.

On the basis of these studies it can be concluded that in order to reliably estimate true BP level, home BP should be monitored at least on 3 days, with duplicate morning and evening measurements. Currently, no consensus exists on recommended home BP measurement schedule. The new information in this thesis could be used to prepare a unified international guideline for home BP measurements. Since the variability of home BP and heart rate are independently associated with future cardiovascular events, home measurements performed on 7 days can provide additional information beyond the basic BP level. Knowledge of the underlying causes affecting morning and evening home BP differences, and of the variability of home BP and home heart rate, will enable healthcare professionals to focus cardiovascular disease-prevention counselling for their patients.

Keywords: home blood pressure, home heart rate, variability, cardiovascular risk

Tiivistelmä

Jouni Johansson. Paras mahdollinen tapa kotiverenpaineen mittausten suorittamiseen sekä verenpaineen ja pulssin vaihtelun kliininen merkitys.Terveyden ja hyvinvoinnin laitos (THL). Tutkimus 66, 178 sivua. Turku, Finland 2011.
ISBN 978-952-245-491-1 (painettu); ISBN 978-952-245-492-8 (pdf)

Kohonnut verenpaine on yksi merkittävimmistä ennenaikaisen kuoleman syistä maailmanlaajuisesti. Tarkka tieto todellisesta verenpainetasosta mahdollistaa tehokkaan ja tarkoituksenmukaisen kohonneen verenpaineen ehkäisyn ja hoidon toteuttamisen. Kotikäyttöön tarkoitettujen verenpainemittareiden helppo saatavuus on mahdollistanut kotona suoritettavat verenpainemittaukset. Hyvin tehty verenpaineen kotimittaus voi olla hyödyllisempi kuin ammattilaisen vastaanotolla tekemä ja sillä saadaan kerättyä suuri määrä tietoa. Tämän väitöskirjan tavoitteena on kehittää optimaalinen verenpaineen kotimittausmalli sekä arvioida kotona mitatun verenpaineen sekä sykkeen vaihtelun itsenäistä merkitystä valtimotautiriskin arvioinnissa.

Väitöstutkimus koostuu kahdesta aineistosta. Finn-home tutkimus perustuu edustavaan suomalaiseen aikuisväestöotokseen (2106, 41-74-vuotiasta henkilöä). Tutkimushenkilöt osallistuivat haastatteluihin, perusteelliseen terveystarkastukseen sekä 7 päivän verenpaineen ja sykkeen kotimittaukseen. Lisäksi Finn-home tutkimuksessa oli mukana seurantatieto henkilöiden sydän- ja verisuonitautitapahtumista. Toinen aineisto koostui 228 iältään 34-64-vuotiaasta Varsinais-Suomessa asuvasta henkilöstä, jotka poimittiin satunnaisesti väestörekisteristä, sekä 236 iältään 35-54-vuotiaasta varsinaissuomalaisesta henkilöstä, joilla oli todettu kohonnut verenpaine. Tutkittavien perusteelliseen terveystarkastukseen kuului sydämen ultraäänikuvaus, virtsan mikroalbumiinin määritys, verenpaineen vuorokausirekisteröinti sekä itse tehdyt 7 päivän kotiverenpaineen mittaukset.

Kotona mitatun verenpaineen yhteys verenpaineen vuorokausirekisteröintiin, kohde-elin vaurioon sekä sydän- ja verisuonitapahtumiin parani kotiverenpainemittausten lukumäärän kasvaessa. Suurin osa tästä paranemisesta tapahtui ensimmäisen 3 päivän aikana. Toisin kuin eurooppalaisissa suosituksissa (2008) todetaan, myös ensimmäisen päivän mittauksia voidaan käyttää, koska ensimmäisen päivän poisjättäminen tekee mittaussuosituksista vaikeaselkoisia.

Verenpaineen- ja sykkeen vaihtelut ennustivat itsenäisesti sydän- ja verisuonitapahtumia. Miessukupuoli, alkoholin suurkulutus, verenpainelääkitys, aikaisempi sydän- ja verisuonitauti ja uniapnea olivat suuremman aamu- ja iltaverenpaineen eron itsenäisiä selittäjiä. Korkea ikä, diabetes, aikaisempi sydän- ja verisuonitauti sekä alkoholin suurkulutus olivat suuremman verenpaineen vaihtelun itsenäisiä selittäjiä. Nuori ikä sekä alkoholin kohtuukäyttö olivat suuremman sykkeen vaihtelun itsenäisiä selittäjiä.
Tämän tutkimuksen perusteella voidaan suositella luotettavan verenpainetason arvioimiseksi verenpaineen mittaamista kotona vähintään 3 päivänä, kaksi kertaa aamulla ja kaksi kertaa illalla. Tällä hetkellä ei ole olemassa yhtenäistä kansainvälistä verenpaineen kotimittaussuositusta. Tämän väitöskirjan tuloksia voidaan käyttää uuden kansainvälisen verenpaineen kotimittaussuosituksen luomisessa. Seitsemän päivän kotimittaukset antavat lisätietoa verenpaineen ja sykkeen vaihtelusta ja ennustavat itsenäisesti sydän- ja verisuonitapahtumia. Tieto verenpaineen ja sykkeen vaihtelun taustalla olevista tekijöistä auttaa terveydenhuollon ammattilaisia sydän- ja verisuonitautien ehkäisyn ja hoidon toteuttamisessa.

Avainsanat: kotona mitattu verenpaine, kotona mitattu syke, vaihtelu, sydän- ja verisuonitauti

Table of Contents

List of original publications

This thesis is based on the following original publications, which are referred to in the text by the Roman numerals.

I **Johansson JK, Niiranen TJ, Puukka PJ, Jula AM.** Optimal schedule for home blood pressure monitoring based on a clinical approach. J Hypertens 2010 Feb;28(2):259-64

II **Niiranen TJ, Johansson JK, Reunanen A, Jula AM.** Optimal schedule for home blood pressure measurement based on prognostic data: the Finn-Home study. Hypertension 2011 Jun;57(6):1081-6

III **Johansson JK, Niiranen TJ, Puukka PJ, Jula AM.** Factors affecting the difference between morning and evening home blood pressure: the Finn-home study. Blood Pressure 2011 Feb;20(1):27-36

IV **Johansson JK, Niiranen TJ, Puukka PJ, Jula AM.** Factors affecting the variability of home-measured blood pressure and heart rate: the Finn-home study. J Hypertens 2010 Sep;28(9):1836-45

V **Johansson JK, Niiranen TJ, Puukka PJ, Jula AM.** Prognostic value of the variability in home-measured blood pressure and heart rate: The Finn-home study. (submitted)

Abbreviations

AAMI	The Association for the Advancement of Medical Instrumentation
ASE	American Society of Echocardiography
ATC	Anatomical Therapeutic Chemical
BHS	British Hypertension Society
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CV	Cardiovascular
ECG	Electrocardiography
ESH	European Society of Hypertension
HR	Heart rate
ICD	International Classification of Diseases, Injuries, and Causes of Death
JNC	Joint National Committee
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
LVMI	Left ventricular mass index
RH	Relative hazard
SD	Standard deviation

1 Introduction

The source of energy required to move blood in the circulation is provided by the pumping action of the heart (cardiac output). Blood pressure (BP) is a measurable end product for an individual's physiological state consisting of the pumping action of the heart and peripheral vascular resistance. More accurately, this includes various factors controlling blood vessel calibre and responsiveness, factors affecting an individual's fluid volume in the circulation and factors affecting cardiac output. All these factors are part of a complex interacting network where a change in one factor affects the others and also the whole system. When the total effect of these factors grows large enough, the result is seen as hypertension. The causes of hypertension are only rarely due to one reason, i.e. a function of only one gene, human internal BP regulation or a few environmental factors, but rather hypertension arises from a combination of a complex interacting network where each of the factors contribute a small effect on BP elevation.

As there are many individual factors contributing to the development of hypertension, it has been shown that an elevated heart rate (HR) is an independent predictor in the development of hypertension [1-2] and, as well, a predictor of all-cause and cardiovascular (CV) mortality in particular [3]. These two facts make HR measurement an interesting and relevant matter to assess. In addition, the easiness in measuring HR at home, in conjunction with BP measurement, makes it even more useful from a clinical perspective.

New studies have brought to light an emerging body of evidence about the causes of hypertension. The effects of environmental factors on BP elevation are of a different scale. Currently, the most remarkable environmental factor influencing the elevation of BP is high dietary sodium (by increasing fluid volume and preload + other mechanisms) [4]. The source of excess sodium in our diets can be tracked back to modern food-processing technology which adds sodium and removes potassium [5]. Obesity, high alcohol consumption and the use of tobacco products elevate BP as well. However, the link between BP elevation and these determinants is diversified (obesity by several mechanisms [6], alcohol by

increasing sympathetic activity + other mechanisms [7] and tobacco by increasing plasma norepinephrine and epinephrine levels + other mechanisms) [8]. Stress has been associated as well with BP elevation (by increasing sympathetic nervous overactivity) [9], but it has been questioned whether or not it causes chronic hypertension [5].
In addition, there are several other reasons such as metabolic and hormonal disorders (diabetes, renal and other internal organ-related causes), physical inactivity, arterial stiffness (and other vascular changes altering the arterial structure), sex hormones and minerals, all of which elevate the CV risk [10].
There are as well genetic factors which have an influence on BP elevation. Several genetic factors elevating BP have been discovered including ethnical differences [11] (e.g. increased salt sensitivity in blacks), obesity-related BP elevation [12] and deletion of angiotensin converting enzyme gene [13]. Since in some studies it has been found that the offspring of hypertensive parents will also develop hypertension [14], there might still be undiscovered genetic forms of hypertension. Genetic studies can help to single out genetic from environmental factors [14], a matter which is crucial in selecting the appropriate therapy for subjects suffering from hypertension.

Regardless of the etiology, hypertension can be classified as primary (essential) hypertension where the cause of blood pressure (BP) elevation is unknown or as secondary when the mechanisms underlying behind BP elevation are known. Over ninety-percent of the cases are classified as primary hypertension [15-16]. However, the frequency of secondary hypertension will progressively increase in time, as improved diagnostic procedures are introduced into clinical use, and as new specific genetic and environmental factors are identified as a cause of hypertension.

Since the prevalence of hypertension in the adult population is currently 26%, and its prevalence is predicted as increasing by 60% by the year 2025 [17], it continues to be an important health-care issue. This has been acknowledged as well by the World Health Organization [18]. In their report, they state that CV diseases are increasing in both developed and developing countries and that the risk factors connected to CV diseases are tobacco use, alcohol consumption, high cholesterol concentrations, high BP levels, low intake of fruit and vegetables, insufficient physical activity and elevated BMI. Of these CV risk factors, high BP ranks at the top together with alcohol.

The prevalence of hypertension in the Finn-Home study (a sub-study of Health 2000 study) by age groups is presented in Figure 1. As enormous amounts of data are currently gathered through BP measurements, the most important goal for the time being is to ensure optimal and reliable BP monitoring, as well as optimal and effective utilization of BP measurement data.

Since the prevalence of hypertension is at a high level in the population and no decline is in view more robust measures should be implemented. The current challenges are to identify those who are at the risk of complications caused by an elevated BP, and to get subjects with an elevated BP to follow recommended lifestyle guidance even in the prehypertension stage. In practice, this means actively promoting home BP monitoring at the population level to reach hypertensive and prehypertensive subjects and to accurately follow and adjust an implementation of lifestyle guidance and antihypertensive medication.

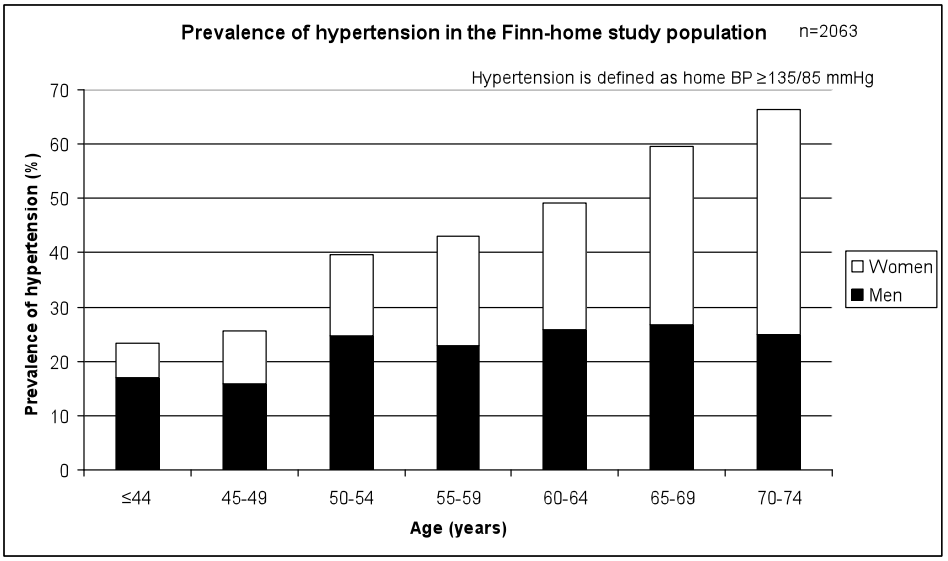

Figure 1. *The prevalence of hypertension by age groups in the Finn-home study.*

Table 1. *JNC-7 criteria for hypertension. Table adapted from [10]*

BP classification	Systolic BP (mmHg)	Diastolic BP (mmHg)
Normal	<120	and <80
Prehypertension	120-139	or 80-89
Stage 1 hypertension	140-159	or 90-99
Stage 2 hypertension	≥160	or ≥100

2 Review of the literature

2.1 Home blood pressure and home heart rate monitoring

For as long as BP has been measured in clinical practice, the auscultatory technique has been the method of choice for the diagnosis and follow-up of hypertension. The first automated home BP monitors as well as the ones used in the office were based on auscultatory technique whereas currently available home monitors are based on oscillometric measurement technique [19].

The introduction of electronic oscillometric home BP monitors and the progressive growth of self-measurement of BP at home have challenged conventional office BP measurement since the latter has some limitations in assessing hypertension and cardiovascular (CV) risk [20]. During the recent decades, cheap and reliable electronical home BP monitors have increasingly found their way to many households as self-measurement of BP has become more popular [21]. According to the above mentioned German study, only in a small amount of patients had the physician encouraged them to perform home BP self-measurements (8%, year 2007). In most of the cases, the impetus was a self-initiative from the patient's side for performing home measurements (78%, year 2007) [21]. A change is needed in the way of thinking in promoting home BP monitoring at population level since the international guidelines have, until now, emphasized office and ambulatory BP monitoring over home BP monitoring.

BP can be monitored at home using either a conventional or an ambulatory BP monitor. However, ambulatory BP monitoring has only found limited clinical use because of its inconvenience and expense compared to home BP monitoring [22]. The barrier between ambulatory and traditional home BP monitoring is slowly fading out as devices with the capacity to perform measurements at predetermined times are being introduced on the market [23], although at present they are not widely commercially available. In addition, however, home BP monitors with embedded monitoring guidelines based on the international

recommendations for monitoring home BP are also being introduced on the market [24].

Home HR is as well, an extremely useful measure, as it is easily achieved in conjunction with home BP measurement. Several studies have found strong associations between BP and HR [25-26]. In addition, there is a growing body of evidence that HR is a predictor of hypertension and also a predictor of all-cause as well as CV mortality [1, 3]. The utilization of home HR in practice is, however, still unclear as its role has not yet been clearly demonstrated in population studies.

In this thesis, I shall focus on how best to monitor home BP. This includes determining the optimal measurement schedule based both on a cross-sectional approach and prognostic data, as well as, factors affecting the difference between morning and evening home BP, and home BP/HR variability. The prognostic value of home BP/HR variability will also be covered in this thesis.

2.2 Technical background of home blood pressure and heart rate monitoring

When the home BP monitors were first introduced into clinical use the majority of monitors were aneroid sphygmomanometer devices [27]. Currently, the device considered as the standard for performing home BP measurement, is a validated automated oscillometric device that records BP from the brachial artery [28]. However, the oscillometric method was first introduced in 1876 [29]. The first commercially produced automated oscillometric device named Dinamap was not on sale till 1976 [30]. It measured only mean arterial pressure. Mean arterial pressure was selected since it is theoretically the most robust measurement (compared to systolic or diastolic pressure) [31]. Several years later the introduction of low-cost microprocessors and pressure transducers allowed the use of other measurement parameters such as systolic and diastolic BP [31].

The oscillometric device's main component and the "workhorse" taking care of the measurement operation is the cuff and its pneumatic connection to the main unit together with pump and valve systems. There can be one or two hoses that connect the cuff pneumatically to the main

instrument. Today the oscillometric devices use a single pneumatic circuit to inflate and deflate the cuff [31].

The cuff is used to compress a limb and its vasculature so as to be able to identify systolic and diastolic blood pressure values from cuff pressure [31]. The inflated cuff compresses the arteries in the forearm so that no blood flow is occurring in the arteries. When the pressure in the cuff is gradually decreased, at some point, the blood begins to flow in the arteries causing oscillations. The point where the artery begins to "emit" the pulsations is where the home BP monitor defines the "maximum BP" called systolic BP. The deflation of the cuff continues until the device can no longer detect oscillations. Pressure in the cuff is sensed by the solid-state pressure transducer and thereafter the signal is postprocessed before it is digitized by analog-to-digital converter. The point where the oscillations disappear, the device defines as the diastolic BP (Figure 2). The microprocessor controls the inflation and deflation process of the cuff and in the end interprets the digital signal.

Every manufacturer of the oscillometric device uses their own algorithm in calculating the correct systolic and diastolic BP values. This information is not publicly available which makes it impossible to thoroughly compare the accuracy of different home BP monitors.

The oscillometric device technique is considered to be cheap and reliable in use compared to other techniques [22]. There are already devices available that have the capacity to store home BP readings in the memory and send them electronically to the physician [32-33]. This further improves patient compliance, BP control and eliminates delays between the patient and the physician. However, the most important issue in selecting a proper home BP monitor is the accuracy of the device. The accuracy of the home BP monitor is ensured by a proper validation protocol which is covered in detail in the next section.

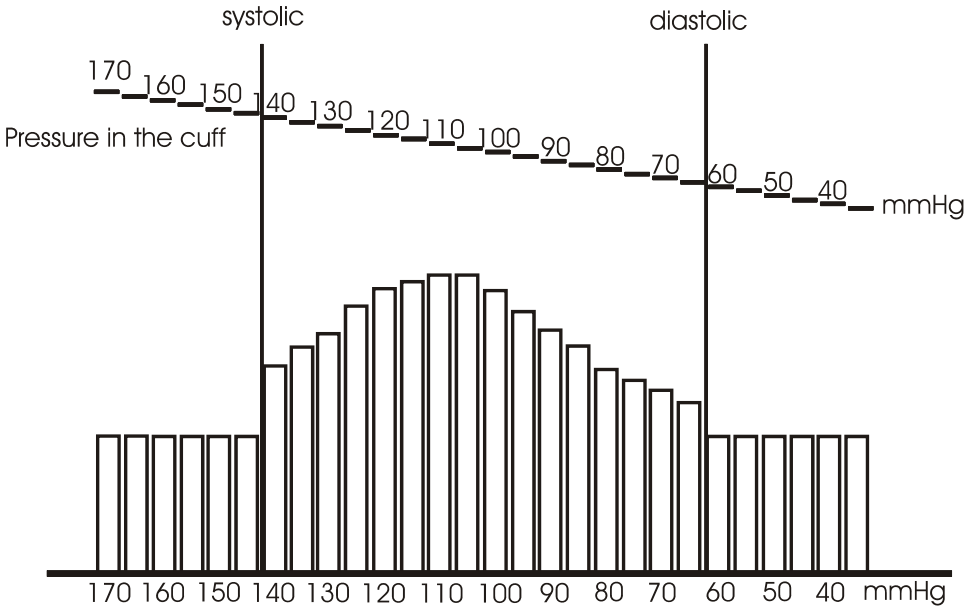

Figure 2. *The figure represents a simplified model on how the oscillometric blood pressure device determines systolic and diastolic blood pressure. The upper lines indicate the pressure in the blood pressure monitoring cuff when it is gradually deflated. The lower bars indicate the oscillations detected by the blood pressure monitor. The first detected oscillation is recognized as systolic blood pressure and the last oscillation the device can detect, is considered to be the diastolic blood pressure.*

2.3 Validation of home blood pressure devices

2.3.1 Validation protocols

BP determination continues to be one of the most important measurements in all clinical medicine but unfortunately it is one of the most inaccurately performed. Since deviations of only a few mmHg may determine whether active measures for lowering the BP are needed or not, accurate measurement of BP is essential to assess the BP related CV risk correctly and to be able to guide the patients with appropriate medication and lifestyle management. For the individual consumers (both medical professionals and laymen), the accuracy of the BP measurement device should be the first priority when selecting a BP monitoring device. The

three most widely used independent validation protocols are those of the British Hypertension Society (BHS) protocol [34], The Association for the Advancement of Medical Instrumentation (AAMI) protocol [35] and the International Protocol of the European Society of Hypertension (ESH) [36]. Between years 2002 and 2009, 104 validation studies had been conducted using the ESH protocol, 36 using the BHS protocol and 28 using the AAMI protocol [37].
In addition, the home BP monitors should be checked for validity at least every second year [22]. Both the BHS and AAMI protocols require an assessment based on 85 subjects, with three BP measurements recorded for each person, for a total of 255 measurements. The idea in both validation protocols is that each monitor-reading is compared with the observer's corresponding reading (performed by a trained human observer using a mercury column sphygmomanometer) and the difference (error) is calculated [38]. There are, however, some differences between the validation protocols regarding the method of the validation of BP monitor-accuracy [38]. The international protocol of ESH is a simplified and rationalized version based on the BHS and AAMI protocols. The main procedures that have been included into the ESH protocol include elimination of pre-validation phases, improving observer recruitment and training, use of simultaneous or sequential comparisons, minimizing observer error during validation and reduction in the number of subjects recruited, relaxing the range of blood pressures, eliminating 'hopeless' devices at an early stage of the validation process, simplifying the validation results, validation algorithm integrity and design modification, diminishing intra-subjects variability by excluding subjects with extremely high or low BPs and taking account of the suitability of the device for individuals [36]. The more detailed differences between ESH and other protocols can be found in the ESH Working Group paper [36].

2.3.2 Limitations of the validation protocols

Consensus reports have suggested that a home BP monitor can be considered valid if it is accurate to within 5 mmHg. This is determined by comparing several readings (usually 255 measurements of 85 patients for AAMI and BHS validation) by an automated monitor and by comparing readings achieved by using a manual sphygmomanometer and a human listener (with a stethoscope) [38]. Although the international validation protocols offer the basis for a unified consensus for home BP monitors,

they have some crucial failures in assessing the error of the home monitors. That is, they analyse the error of the 255 individual readings and not the errors observed in 85 participants. Therefore, the protocols do not take account of the between-individual variability in the validation process. Due to this reason, a home monitor can be more accurate for some individuals than for others. It has been recommended that the validation process should contain two stages: first, the BP monitor should be validated at the population level, and second, the same monitor should be validated for the individual user [38].

Health care personnel and individuals can find a continuously updated list of currently validated monitors for self-measurement of BP at www.dableducational.org.

2.4 Morning and evening measurements in home-measured blood pressure

Current international guidelines recommend measuring home BP twice every morning and evening. However, BP is not a constant variable and variation throughout the day occurs. In a healthy, normotensive European general population evening home BP is higher than morning home BP [39-42]. In contrast to studies made in Europe, Japanese population studies show that in the general population morning home BP is higher than evening home BP [43-46]. Because of the differences in populations and reasons behind these phenomena, it is important to know the factors affecting the morning-evening difference of home BP. Harmful effects of high morning BP (morning surge) have been linked to CV (strokes) diseases independent of the 24-hour BP level [47] and to sleep apnea [48], but the factors affecting the difference of morning and evening BP have remained partly unknown.
Some studies have tried to assess the characteristics and factors affecting morning-evening difference [43-46]. However, more detailed information is needed especially about the lifestyle factors affecting the morning-evening difference. The knowledge of the exact lifestyle factors affecting this difference would help physicians to easily recognize individuals by their morning and evening BP profile.

2.5 Variability in home-measured blood pressure and heart rate

BP and HR are not constant variables and significant fluctuations occur throughout the day and also during longer periods of time. The variation in home-measured BP and HR can be caused by two reasons, firstly by the errors of the home BP monitor, and secondly by the physiological variation in humans. Variation of BP and HR are affected by physiological factors: e.g. respiration, emotions, physical exercise, activity of the alimentary system, hormonal regulation and fluid balance (absolute volume and concentration), and by extrinsic factors such as: tobacco products, alcohol, the atmosphere, temperature, pain, antihypertensive drugs, as well as other lifestyle factors [49]. In addition, BP and HR variations can be classified as ultra-short time (beat-to-beat), intraday (between daily measurement occasions), diurnal (morning-evening) and long-term (e.g. day-to-day or seasonal) BP or HR variability.

The harmful effects of high (home) BP and HR on health are well known, but the factors affecting the variability of home-measured BP and HR have, however, remained unclear. In addition, the knowledge of the prognostic value of the variability in home-measured BP and HR are still imperfect, as no studies exist based on the current recommended monitoring guidelines (including 7 days consecutive BP monitoring with two morning and two evening measurements) [49-50].

The significance of the variability in ambulatory BP and HR has been well studied and the results have provided evidence that the variability of BP and HR have both diagnostic and prognostic value [51-59]. Different patterns in BP and HR variability have been associated with sympathetic nervous regulation, alcohol use, target-organ damage and CV events [51-59]. However, the significance of the variability in home-measured BP and HR has remained quite unknown. Currently, only one study has been made about the prognostic value of day-by-day home BP variability in which greater day-by-day morning home BP variability predicted CV mortality [60]. However, no studies have been made assessing the value of the variability in home-measured BP and HR according to the recommended current international guidelines [49-50]. Therefore, the prognostic value of the variability in home-measured BP and HR have until now remained unclear.

2.6 Benefits of home blood pressure monitoring

2.6.1 Home-measured blood pressure advantages over clinic and ambulatory blood pressure monitoring

The use of self-measurement of BP at home has become widely popular because of the easiness of its use compared to ambulatory recordings and it obtains better assessment for the severity of hypertension and prediction of risk than by using clinical measurements [20]. Measuring blood pressure at the clinic is limited by the small number of readings usually taken and the poor estimate of the individual's true BP level.
Home BP measurement is as reliable as ambulatory BP measurement in assessing hypertension and target-organ damage [61-63]. However, for an extra benefit, ambulatory measurement even provides information of the 24-hour BP profile as well as short-term variation. Especially nighttime BP has been found to be a better predictor of CV risk than daytime BP [64-67]. Ambulatory BP monitoring has only a limited clinical use because it is inconvenient and expensive. Therefore, ambulatory recordings are best suitable for specific group of individuals. This includes individuals who are unable to perform home BP measurements according to the recommended guidelines. In clinical practice, ambulatory and home BP monitoring complement each other.

Home BP measurement provides more accuracy over clinical BP by easily enabling a large number of home readings [68]. In addition, home BP readings are not affected by white-coat effect [69] and are therefore suitable for subjects suffering from 'white-coat effect'. Home BP monitoring is often also the best available method for assessing BP in special groups of individuals, such as in subjects with diabetes, chronic kidney disease, elderly individuals, as well as in pregnant subjects [49-50]. Furthermore, home BP measurements can be used effectively to monitor the antihypertensive drug efficacy [70-72]. Using home BP monitoring can also improve control of hypertension by giving an active role to the individual himself [73]. Coupling home BP monitoring with telemedicine can further improve hypertension control [74-76].

2.6.2 Economical benefits

Home BP monitoring makes it possible to gather large amounts of data easily and at a low cost compared to other methods (office or ambulatory monitoring) [77]. Moreover, in several prognostic studies, home BP monitoring has been proved to be as good as ambulatory BP monitoring and even better than office monitoring [20, 61-63]. In two studies examining the compliance of home BP monitoring it has been shown that possession and use of home BP monitor improves patient knowledge concerning BP control, enabling better decisions and promoting confidence in BP management [78-79]. Furthermore, it has been found that subjects who had home BP monitoring had lower BP than those who did not [80].

Even though home BP monitoring has been adapted for use worldwide, its cost-effectiveness has not been thoroughly investigated. Some studies on that subject have, however, been made [81-82]. Home BP monitoring has a huge potential for cost savings in medical economy since it can prevent unnecessary treatment of subjects having the white coat phenomenon, and may curb unnecessary office visits [81-82]. However, home BP monitoring can also lead to worse BP control compared to office BP monitoring [82].

2.6.3 Individual benefits

Today, there is a growing interest in finding new ways of helping people to become interested in their own health not just momentarily but throughout their whole life. This means that medical professionals should be familiar with the newest strategies available in preventive health care.

One intervention in achieving effective health advances is to get patients sympathetic to the idea of self-care. Great strides are made when patients are taking an active part and give their own contribution to their health promotion. By focusing on self-care and prevention of CV diseases, home BP monitoring offers remarkable individual benefits over other techniques [75].

The American Heart Association, the American Society of Hypertension and the Preventive Cardiovascular Nurses Association have also made a joint scientific statement concerning both the economical and individual benefits of home BP monitoring [50].

2.7 Limitations of home blood pressure and heart rate measurements

Home BP monitoring provides a robust method for reliably assessing BP level in the general population and that is why there is a widely accepted common agreement that home BP monitoring should be used for all patients with a BP problem. However, there are still some marginal limitations where home BP monitoring is not suitable. These limitations include specific group of individuals: subjects who are unable to follow instructions of home BP self monitoring (e.g. demented subjects), subjects who are easily stressed about performing self measurements, subjects with atrial fibrillation or other arrhytmias (when the oscillometric device cannot perform the measurements reliably), and when 24h BP profiles are needed, that is, quantification of nocturnal BP (dippers and nondippers) and short-term BP variability. Moreover, there might be some user-related techniques that can cause difficulty for an oscillometric device to perform BP measurements correctly. These are cuff-related causes (incorrect cuff size, incorrect cuff application and leaking cuff or hoses) and patient-related causes (cuff not at heart level and patient not instructed to relax properly before measurement) [31]. The features between home, office and ambulatory BP monitoring are compared in Table 2.

Despite the fact that home BP monitoring provides a valid representation of the patient's true BP level, more focus should be put on the patient's valid documentation of home BP in clinical care [83]. In addition, although there is an increasing rate of self-monitoring of BP [21], only 60% of the hypertensive patients in Finland use home BP monitoring regularly [84]. Therefore, more effort should be focused on the promotion of proper home BP monitoring use and on improving the accessibility of home BP monitoring data. At the same time, to ensure reliable home BP monitoring, doctors should be aware of recommending only validated home monitors to their patients.

As there is a growing body of evidence that an elevated HR is as well a risk-factor for hypertension and CV mortality [1, 3], the value of home HR measurements have not yet been recognized. As home HR

measurement is easily performed in conjunction with home BP monitoring, the obstacle to its current utilization has been the lack of studies giving proof of its value.

Table 2. *Comparison between features of home, office and ambulatory monitoring*

Feature	Home monitoring	Office monitoring	Ambulatory monitoring
Treatment assessment	Easy	Easy	Laborious
White coat effect	No	Yes	No
Reproducibility	High	High	High
24-hour recording	Possible	No	Yes
Morning measurement	Yes	Difficult	Yes
Evening measurement	Yes	Difficult	Yes
Long term variability	Yes	Difficult	Difficult
Day-by-day variability	Yes	Difficult	Difficult
Beat-to-beat variability	No	No	Yes
Prognostic value of CV events	High	Low	High
Patient compliance	High	Low	Low
Hypertension control	High	Moderate	Low
Cost	Low	Moderately high	High

2.8 Current international recommendations for home blood pressure monitoring

The European Society of Hypertension guidelines, the Japanese Society of Hypertension and the American Heart Association statement for home BP monitoring currently recommend that home BP should be monitored preferably for 7 days with two morning and two evening measurements [49-50, 85]. The average of all values should be used with the exception of the first day values which should be discarded. It has also been discussed whether the first-day home BP values should be discarded or not [86]. The guidelines recommend discarding the first-day home BP measurements as they may be higher and more unstable (higher variation) than the measurements performed on the following days [49-50, 86]. The same statement and the guidelines also give monitoring-preparation recommendations for individuals performing home BP measurements. Tobacco or caffeine containing products should be avoided for 30 minutes before the measurements, and the measurements should be performed after 5 minutes of rest. The more specific recommendations can be read in the above-mentioned references. Also available is a concise version of the current European Society of Hypertension guidelines intended to be used by clinicians in daily practice [87].

The American Heart Association statement and The European Society of Hypertension guidelines provide a good practical methods of how to evaluate and deal with different kinds of patient types, e.g. subjects with diabetes, elderly, chronic kidney disease, pregnant subjects and subjects using antihypertensive medication [49-50]. This is highly important since home BP monitoring is being increasingly used in many countries and among different subjects.

The current statement and the guidelines also take account of the cost-effectiveness of home monitoring versus other techniques.

2.9 Evaluating blood pressure and cardiovascular risk in clinical practice

According to current international guidelines [49-50] the target goal for home BP is <135/85 mmHg or <130/80 mmHg in high-risk patients (only American guidelines). When home BP is measured according to currently recommended guidelines using a validated measurement device, the patient risk evaluation can be performed correctly.

Accurate and real home BP level achieved by carefully following the measurement protocol and combined with a major risk-factor profile of an individual patient (made through examining medical history, physical examination, laboratory and other necessary diagnostic tests) gives a thorough image of the risk which the patient is exposed.

The most essential CV related risk factors including hypertension are old age (>55 years for men and >65 years for women), diabetes mellitus, a family history of premature CV disease (<55 for men and <65 for women), obesity, physical inactivity, dyslipidemia, and probable target-organ damage (LVH, microalbuminuria, myocardial infarction, heart failure, stroke, chronic kidney disease) [10, 88].

By using the above-mentioned methods in the evaluation of the CV risk of an individual patient provides the physician ability to take correct measures on CV risk-management (reveal identifiable individual causes of hypertension, apply antihypertensive therapy if necessary and give CV risk prevention counselling).

CV risk evaluation can either be based on surrogate end-points including assessment of LVH (using echocardiography or ECG), microalbuminuria and carotid ultrasonography or CV events data (morbidity or mortality). Surrogate end-points are often easier to assess, but mortality data provide better risk-prediction accuracy.

Computer-based calculators for CV risk evaluation have been developed by several instances (e.g. FINRISKI and Framingham). They are based on the risk-factor characterization of the patient, that is: age, gender, laboratory data, BP level and family history of CV disease. These calculators make the evaluation of CV risk possible in clinical practice in a fast and efficient way. However, for the time being a disadvantage related to these calculators are that their database is based on the office BP measurements and not on home BP measurement data. In order to efficiently and reliably implement a CV risk calculator, it should be based on home BP measurements, with up-to-date CV risk-factor data.

2.10 Goals of home blood pressure monitoring

The most fundamental goal of home blood pressure monitoring is to diagnose those who are at the greatest CV risk. This is not only done by measuring the BP level itself but also by utilizing other information obtained from home BP measurements (BP and HR variability and HR level). Since the current guidelines on home BP monitoring are still far from perfect, in this thesis I shall focus on how best to monitor home BP. This includes determining the optimal measurement schedule based both on the cross-sectional approach and on the prognostic data, as well factors affecting the difference between morning and evening home BP, and home BP/HR variability. The prognostic value of home BP/HR variability will also be covered in this thesis.

3 Aims of the study

This thesis was set out to build an optimal measurement schedule for home blood pressure monitoring, and to investigate the use of home BP variability and home HR variability in primary health care.

The specific goals were:

1. To find an optimal schedule for home blood pressure measurement based on the association between home blood pressure and target-organ damage and between home blood pressure and ambulatory blood pressure measurements.

2. To find an optimal schedule for home blood pressure measurement based on prognostic value.

3. To examine the determinants affecting morning and evening home blood pressure difference.

4. To study the determinants affecting the variability of home-measured blood pressure and heart rate.

5. To assess the prognostic significance of variability in home-measured blood pressure and heart rate.

4 Materials and methods

In the following paragraphs the materials and methods of Studies I-V are covered. Studies II-V are based on the Health 2000 studies where as Study I is based on 2 cohorts consisted of the general population and the hypertensive population.

4.1 General

Figure 3 describes the home BP measurement scheme used in Studies I-V. Home BP was measured on 7 consecutive days, twice in the morning and twice in the evening, yielding altogether 28 measurement points. Variability variables are only used in Studies IV and V. The BP/HR variability variables are based on the calculation of SD. The formulas of morning minus evening home BP/HR variability, first minus second measurement of home BP/HR variability and morning/evening day-by-day home BP/HR variability are presented below. The parameters of home BP/HR variability have been chosen so that they represent clinically relevant variability components.

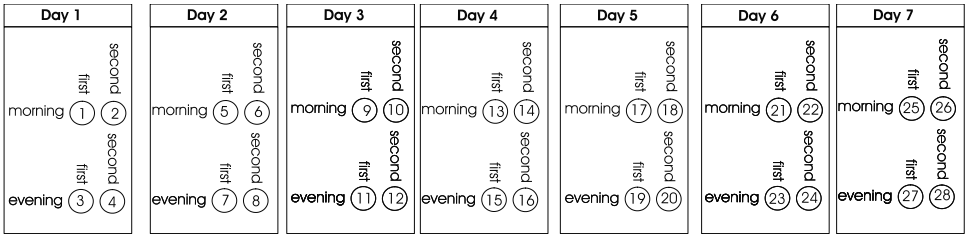

Figure 3. *Home blood pressure measurement schedule. Numbers inside the circles indicate the individual measurement points.*

Morning minus evening home BP/HR variability

SD of the following differences between morning and evening measurements

$$\left(\bar{x}_{1,2} - \bar{x}_{3,4}\right)\left(\bar{x}_{5,6} - \bar{x}_{7,8}\right)\left(\bar{x}_{9,10} - \bar{x}_{11,12}\right)\left(\bar{x}_{13,14} - \bar{x}_{15,16}\right)\left(\bar{x}_{17,18} - \bar{x}_{19,20}\right)\left(\bar{x}_{21,22} - \bar{x}_{23,24}\right)\left(\bar{x}_{25,26} - \bar{x}_{27,28}\right)$$

First minus second home BP/HR variability

SD of the following differences between the first and second measurements

$$(\bar{x}_{1,3} - \bar{x}_{2,4})(\bar{x}_{5,7} - \bar{x}_{6,8})(\bar{x}_{9,11} - \bar{x}_{10,12})(\bar{x}_{13,15} - \bar{x}_{14,16})(\bar{x}_{17,19} - \bar{x}_{18,20})(\bar{x}_{21,23} - \bar{x}_{22,24})(\bar{x}_{25,27} - \bar{x}_{26,28})$$

Day-by-day home BP/HR variability

SD of the following mean values between seven individual days

$$\bar{x}_{1,2,3,4}, \bar{x}_{5,6,7,8}, \bar{x}_{9,10,11,12}, \bar{x}_{13,14,15,16}, \bar{x}_{17,18,19,20}, \bar{x}_{21,22,23,24}, \bar{x}_{25,26,27,28}$$

Morning day-by-day home BP/HR variability

SD of the following mean values between seven individual days morning measurements

$$\bar{x}_{1,2}, \bar{x}_{5,6}, \bar{x}_{9,10}, \bar{x}_{13,14}, \bar{x}_{17,18}, \bar{x}_{21,22}, \bar{x}_{25,26}$$

Evening day-by-day home BP/HR

SD of the following mean values between seven individual days morning measurements

$$\bar{x}_{3,4}, \bar{x}_{7,8}, \bar{x}_{11,12}, \bar{x}_{15,16}, \bar{x}_{19,20}, \bar{x}_{23,24}, \bar{x}_{27,28}$$

$\bar{x}_{k_1,\ldots,k_n}$ = mean of *n* number of individual home BP/HR measurement points. Subscript of *k* indicates the individual measurement order number (from 1 to 28).

4.2 Study I

4.2.1 Study population

The study population consisted of 2 cohorts. The study sample for the first cohort consisted of 340 men and women aged 34−64 years living in southwestern Finland who were randomly drawn from the population register. 275 subjects (80.9%) agreed to participate in the study. After excluding subjects with diagnosed coronary artery disease, cerebrovascular disease, insulin-treated diabetes mellitus, hemodynamically significant valvular disease, pregnant women, subjects with antihypertensive medication and those who had performed under 14 home BP measurements, the first study cohort consisted of 228 subjects.

The study sample for the second cohort consisted of 252 newly diagnosed, but yet untreated, moderately to severely hypertensive men and women, aged 35−54 years. These patients were referred to the study by general

practitioners and internists within the primary and occupational health services in southwestern Finland. The inclusion criteria were a systolic BP consistently between 180 and 220 mmHg, or a diastolic BP between 100 and 120 mmHg, as measured within the primary healthcare system. Recruitment BP was defined as the mean of the last 2 measurements made by the primary healthcare staff. Patients with coronary artery disease, cerebrovascular disease, insulin-treated diabetes mellitus, or hemodynamically significant valvular disease and pregnant women were excluded from the study. In addition, subjects who had performed under 14 home BP measurements or had started taking antihypertensive medication before the study were excluded. The second study cohort consisted of 236 subjects.

The two cohorts were analysed both separately and together (n=464). The study was conducted in compliance with the Second Declaration of Helsinki and was approved by the ethical committee of the Social Insurance Institution of Finland. All the subjects gave their informed consent.

4.2.2 Flow of Study I

The flow chart of the population in Study I is presented in Figure 4.

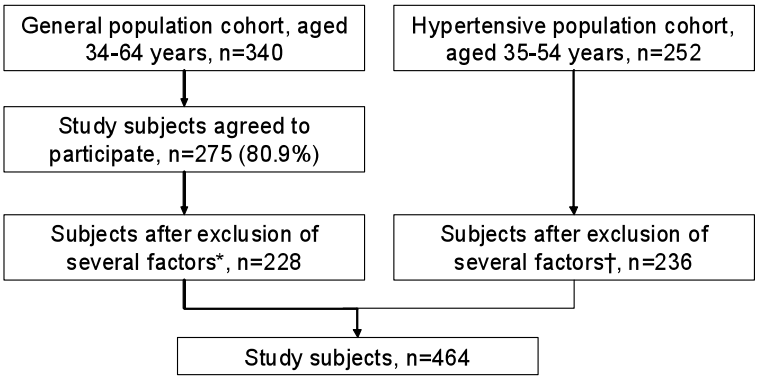

Figure 4. *A flow chart of the study population in Study I.*
** Subjects who had been diagnosed as having coronary artery disease, cerebrovascular disease, insulin-treated diabetes mellitus, hemodynamically significant valvular disease, pregnant women, subjects with antihypertensive medication and those who had performed under 14 home BP measurements were excluded.*
† Patients with coronary artery disease, cerebrovascular disease, insulin-treated diabetes mellitus, or hemodynamically significant valvular disease, pregnant women and patients who had performed under 14 home BP measurements were excluded.

4.2.3 Urine microalbumin

24-h urine was collected for albumin measurements. The measurement range for albumin was from 0.5 to 16 mg/dL and the amount of albumin was measured by nephelometry (Orion Diagnostica 667560, Orion corp., Finland).

4.2.4 Echocardiography

To assess the left ventricular mass (LVM) the echocardiography examinations were successfully performed for 494 subjects using 2-dimensional controlled M-mode examinations (Aloca SST-860 color Doppler ultrasonoscope and a 3.5 MHz phased-array transducer). Measurements were performed according to the recommendations of the American Society of Echocardiography (ASE) [89]. Left ventricular echocardiograms were measured at the tips of mitral leaflets and averaged over 3 heart cycles. ASE cube left ventricular mass (g) was calculated as follows: 1.05 x [(interventricular septal thickness in diastole + left ventricular internal dimension in diastole + posterior wall thickness in diastole)^3 – (left ventricular internal dimension in diastole)^3]. Corrected left ventricular mass (g) was calculated by the Devereux equation 0.8 x (ASE cube left ventricular mass) + 0.6 [90].
The LVM index (LVMI) in this study was defined as [LVM (g) / height (m)].

4.2.5 Home blood pressure measurements

The BP self-measurements were performed at home on 7 consecutive days, twice in the morning and twice in the evening by using a validated automatic oscillometric device (Omron HEM 705C, Omron Matsusaka Co, Japan) [91]. The participants measured their blood pressure between 0600 and 0900h in the morning and between 1800h and 2100h in the evening. The two measurements were performed at 1−2 minutes intervals. The participants received oral and written instructions on how to perform the home BP measurements correctly and the 7-day home BP monitoring commenced on the following morning. The mean number of home BP measurements was 27.5 ± 1.6.

4.2.6 Ambulatory blood pressure monitoring

Ambulatory BP was recorded using an automatic Suntech Accutracker II (Suntech Medical Instruments, Raleigh, NC, USA) unit set to take measurements every 15 minutes during the daytime (between 0600 and 2300h) and every 30 minutes during nighttime (between 2300 and 0600h). Measurements were performed according to the guidelines of the Berlin

Consensus Document [92]. Mean 24-hour ambulatory BP was used for all analyses.

4.2.7 Statistical analysis

The statistical analyses were performed with SAS software version 9.1 (SAS Institute, Cary, NC, USA). The means of the systolic BP and diastolic BP were calculated both separately and cumulatively for individual days. Before the statistical analyses were performed, the skewed distribution of urine microalbumin was corrected by a logarithmic transformation (natural logarithm). Pearson's correlation was used to describe the association between continuous variables. The comparisons between the correlations were performed using SAS Calis procedure.

4.3 Studies II-V

4.3.1 Study populations

These studies are part of the multidisciplinary epidemiological survey, the Health 2000 Study, which was performed in Finland from autumn 2000 to spring 2001. The Health 2000 Study population was a stratified two-stage cluster-sample composed of 8028 individuals randomly drawn from the population register representing Finnish adults aged 30 years or over. The details of stratification and sampling procedures have been previously reported [93].

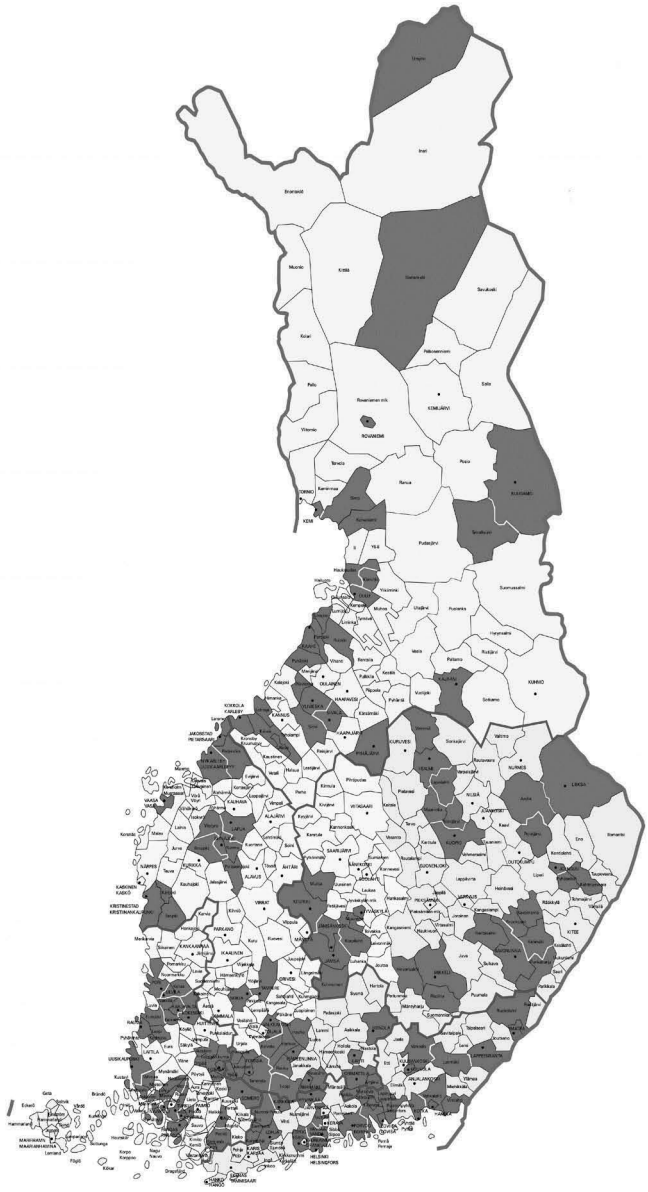

Figure 5. *Study locations of the Health 2000 study are marked in dark grey on the map of Finland.*

There were 4934 individuals aged 41—74 years, of which 4148 (84%) agreed to participate in the interview and also attended the health

examination. Finally, 2106 individuals participated in the home BP measurement substudy (Finn-home study). The study participants with arrhytmias such as atrial fibrillation and flutter were not included in the Finn-home study. Home measurement of BP was not performed on all individuals willing to participate because of the limited number of home monitors (approximately 800). The home monitors were given to the study participants in random order. The study protocol of the Health 2000 Study was approved by the Epidemiology Ethics Committee of the Helsinki and Uusimaa hospital region, and all participants gave their signed informed consent.

Subjects of the Finn-home substudy who had a missing health examination or interview data (n=25 in Study II; n=153 in Studies III and IV; n=191 in study V), had not performed 14 or more valid home measurements of BP (n=38, in Study III), had not performed 14 or more valid home measurements of BP or HR (n=50, in Studies IV and V), or had incomplete laboratory values (n=11, in Studies III, IV and V) were excluded from the study. After removing participants with one or more exclusion factors, the study population consisted of 2081 (in Study II), 1919 (in Study III), 1908 (in Study IV), and 1869 (in Study V) participants.

Nonparticipants consisted of those who agreed to go to the interview and attended the health examination, but did not participate in the home BP measurement study or were excluded from the participants' group. Nonparticipants differed slightly from the participants (aged 41-45 years and 45-74 years) included in the Finn-home substudy, in terms of age, systolic office BP, use of antihypertensive medication and prevalence of diabetes (Table 3). Furthermore, participants aged 41-74 years differed from nonparticipants in terms of BMI.

Table 3. *Participants versus nonparticipants.*

Variable	Participants (n=2012)†	Participants (n=2106)‡	Nonparticipants (n=1721)§	p*	p**
Age (years)	56.9 (8.3)	56.3 (8.5)	58.0 (8.7)	<0.001	<0.001
BMI (kg/m²)	27.5 (4.5)	27.4 (4.5)	27.8 (5.0)	0.07	0.026
Alcohol use (g/wk)	77.7 (146.6)	79.3 (146.8)	73.1 (157.3)	0.37	0.23
Systolic Office BP	137.9 (20.3)	137.4 (20.2)	140.8 (21.6)	<0.001	<0.001
Diastolic Office BP	83.8 (10.7)	83.7 (10.7)	84.3 (11.1)	0.17	0.12
Office HR	67.3 (10.8)	67.3 (10.7)	67.4 (11.3)	0.63	0.62
Male (%)	931 (46.3)	980 (46.5)	794 (46.1)	0.93	0.81
Smokers (%)	470 (23.4)	506 (24.0)	405 (24.8)	0.31	0.58
Antihypertensive medication (%)	596 (31.9)	604 (30.9)	608 (35.3)	0.03	0.0046
Diabetes (%)	136 (7.3)	137 (7.0)	145 (9.5)	0.021	0.0084

BMI, body mass index; BP, blood pressure; HR, heart rate

Values are expressed as mean (SD) or numbers (%) as appropriate.

* Participants (n=2012) vs. nonparticipants

** Participants (n=2106) vs. nonparticipants

† Participants aged 45-74 years

‡ Participants aged 41-74 years

§ Nonparticipants aged 45-74 years

4.3.2 Flow of the studies (Studies II—V)

The flow chart of the population in Studies II-V is presented in Figure 6.

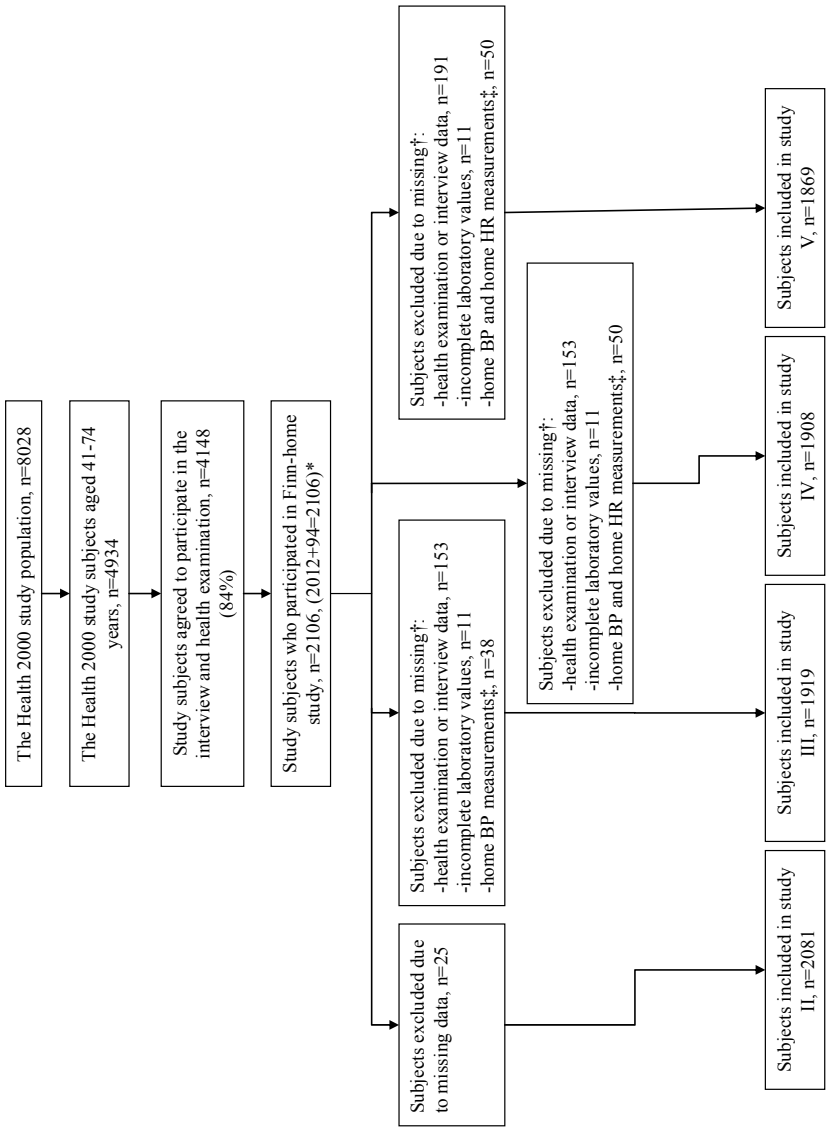

Figure 6. *A flow chart of the study population in Studies II-V.*
** There were 94 participants aged <45 years (2 subjects aged 41 years, 1 aged 42 years and 91 aged 44 years).*
† Some excluded subjects have more than one exclusion factors missing.
‡ Less than 14 home BP and/or home HR measurements performed.

At an initial health interview at the participant's home, basic background and sociodemographic information, information about health and illnesses as well as the use of medication was gathered by centrally-trained interviewers. Individuals who were willing to participate in the Finn-home substudy received home monitors for measuring BP and HR during the week after the health interview. A physical examination was performed on each participant 1—6 weeks later at a local health centre by centrally-trained doctors and nurses. Each participant's height, weight, and body circumference were measured, and fasting blood samples for serum lipids and glucose were taken from the participants. Details of the methodology of the project have been published elsewhere [93-94].

4.3.3 Home blood pressure and home heart rate measurements (Studies II—V)

Home BP and HR were self-measured with a validated, automatic oscillometric device (Omron model HEM-722C; Omron Corp., Tokyo Japan) [95]. Participants received written instructions and individual guidance on how to measure BP and HR correctly. Seated BP and HR were measured twice, approximately at a 2-min interval every morning between 0600 and 0900 h (before breakfast and washing) and every evening between 1800 and 2100 h on 7 consecutive days. Study participants were informed to avoid smoking (or other tobacco-containing products), caffeine-containing products, heavy physical exercise and eating before measurements. Before the measurements, study participants were instructed to sit in a straight chair by a table for at least 10 min, with a BP monitoring cuff wrapped around the upper arm for at least 5 min. Home BP and HR were determined as the mean of 14 duplicate measurements (28 measurements). A sum of 86.3% of the study population had complete home monitoring data (all 28 measurement points). Ninety-eight percent of the study population had at least 14 monitoring points. The mean number of home BP and HR measurements were 26.7 ± 3.7 (Study II) and 27.0±2.8. (Studies III-V).

4.3.4 Office blood pressure measurements (Study III)

Office BP was measured by a nurse with a conventional and calibrated mercury sphygmomanometer from the sitting individual's right arm after 10 min of rest. The last 5 min of rest were spent in the measuring room with the cuff around the upper right arm. BP was measured using a pressure cuff of appropriate size and methods that were in accordance with current guidelines [96]. Systolic and diastolic BP were defined according to Korotkoff sounds I and V. The means of two measurements performed at a 2-min interval were used to determine office BP.

4.3.5 ECG measurements (Study III)

Standard resting 12-lead ECGs were digitally recorded by using a Marquette MAC 5000 device and stored as digital data on a Marquette MUSE CV 5B system (Marquette Hellige, Milwaukee, WI, USA). All ECGs were overread, and the measurements corrected if needed, by a single physician experienced with ECG before being stored into the database. ECG-left ventricular hypertrophy (LVH) was assessed with Cornell product ($[R_{aVL}+S_{V3}]$ x QRS duration, plus 6 mm for women) [97], because it had the highest correlation with home BP [98].

4.3.6 Definitions

Diabetes mellitus was defined as a fasting serum glucose level higher or equal to 7.0 mmol/l (one measurement was available) or the use of insulin injections, oral hypoglycaemic agents or both (Anatomical Therapeutic Chemical (ATC) codes A10A and A10B). Presence of hypercholesterolemia was defined as a fasting serum total cholesterol level higher or equal to 7.0 mmol/l, or the use of lipid modifying agents ATC code C10A). Smoking was defined as current use of tobacco products (yes or no). Alcohol intake was evaluated with a questionnaire and the amount of alcoholic drinks was converted to grammes of absolute ethanol. Because of the large portion of abstinent participants (n=577, 30%), alcohol consumption (g/week) was divided into three groups according to international recommendations [99-100]. The first group

included the participants who did not use alcohol, the second group included men using over zero and less than or equal to 280 g/week and women over zero and less than or equal to 140 g/week and the third group included men using over 280g/week and women over 140g/week, respectively.

A questionnaire was used to define the occurrence of sleep apnea according to following criteria (Studies III and IV) [101]. If the answer to the question 'Do you snore when sleeping? (Ask others if you are not sure)' was 'yes', then the following additional questions were addressed: 'How often do you snore'?, 'What does your snoring sound like? (Ask others if needed)' and 'Have you noticed (or have others noticed) respiratory pauses when you sleep'?. Sleep apnea was considered probable, if snoring was loud and irregular, with occasional respiratory pauses, stertorous breathing or both; and respiratory pauses with a frequency of at least 1—2 nights weekly. Using these criteria, apnea was found in 179 participants (10%).

The selection to normal, prehypertensive and hypertensive category was made by office BP measurements according to Joint National Committee 7 (JNC-7) criteria [10] (Study III). Stage 1 and stage 2 hypertension categories were combined as one hypertension category.

A history of CV disease was defined as having at least one of the following: past history of angina pectoris, heart infarction or stroke. In addition to these, previous percutaneous coronary intervention or coronary artery bypass graft surgery was also included in the history of CV disease in Study V. Information on previous myocardial infarction, coronary heart disease, strokes, percutaneous coronary intervention or coronary artery bypass graft surgery was obtained from hospital discharge summaries that study participants brought along, or from the National Hospital Discharge Register.

4.3.7 Follow-up

The follow-up data were accumulated until December 31, 2008 (Study V), and until December 31, 2007 (Study II). Mortality data were obtained from the national mortality register based on death certificates. The 10th version of the International Classification of Diseases, Injuries, and

Causes of Death (ICD-10) was used in classification. ICD-10 codes I21-I25 (chronic or acute ischemic heart disease), I61 (intracerebral hemorrhage), I63 (cerebral infarction), I46 (cardiac arrest), I11 (hypertensive heart disease), I71.3 (ruptured abdominal aortic aneurysm), and I70.2 (atherosclerosis of extremity arteries) were classified as CV deaths.
Data on hospitalization due to heart failure and non-fatal coronary and stroke events were obtained from the national hospital discharge register. Non-fatal CV events included the following events: ICD-10 codes I21-23 (acute coronary events), I61 and I63 (acute stroke events), and I50 (hospitalized due to acute heart failure). In addition, the performed coronary interventions and coronary artery bypass-graft surgeries were obtained from the hospital discharge register. The Finnish hospital discharge register and national mortality register data have been validated on stroke and coronary heart disease diagnoses [102-103].
The primary endpoint was the combination of CV mortality, non-fatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, percutaneous coronary intervention, and coronary artery bypass surgery. Only the first event was included in the analysis. The secondary end-point was total mortality.

4.3.8 Statistical analyses

The variability of home BP and HR are calculated as the SD of daily morning minus evening measurements of 7 consecutive days (morning—evening home BP and HR variability), as the SD of daily BP mean of 7 consecutive days (day-by-day home BP and HR variability) and as the SD of all the first minus second measurements (1st—2nd measurement of home BP and HR variability) (Figure 3). The skewed distributions of all home BP variability and HR variability variables were log-transformed for the analyses. Pearson's correlation was used to assess the relationship between home BP and HR variability and continuous variables. Student's t-test was used to compare the between-group differences in home BP and HR variability. Analysis of variance was used to compare home BP and HR variability between groups divided by alcohol consumption. Statistically significant variables in the univariate analyses were included in the multivariate linear regression analysis (Studies III and IV).
The Cox proportional hazards' model was used to test the association between CV events and individual covariates (age, gender, BMI, home

BP/home HR, presence of diabetes, current smoking, use of alcohol, presence of hypercholesterolemia, past history of CV disease and use of antihypertensive medication) (Study V). The Cox proportional hazards' model was used as well for prognostic multivariate analyses (Studies II and V). Association of home BP variability and home HR variability with the end-points were analysed by estimation of the relative hazard ratios (RH) and their 95% confidence interval (CI) per 1 mmHg or 1 beat/min increase in the variability of BP or HR (Study V). The prognostic models were adjusted for age, gender, BMI, home BP/home HR, presence of diabetes, current smoking, use of alcohol, presence of hypercholesterolemia, past history of CV disease and use of antihypertensive medication (Study V). The likelihood ratio χ^2 value was used as a measure of goodness of fit between the model containing a single BP index and the model containing 2 indices (Study II). A significant likelihood ratio χ^2 indicates that the index represents a significantly stronger association with CV events (Study II).
Statistical analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, North Carolina, USA. A p-value of less than 0.05 was considered statistically significant.

5 Results

5.1 Optimal schedule for home blood pressure monitoring (I and II)

5.1.1 Characteristics of home blood pressure during 7 consecutive days of measurement (I)

Mean evening systolic/diastolic home BP was 3.7/1.2 mmHg higher than mean morning home BP ($p<0.001$ for both). The mean of the first systolic/diastolic home BP measurements on each measurement occasion was 2.3/1.2 mmHg higher ($p<0.001$ for both) than the mean of the second measurements. BP averaged over days 2 through to 7 was only 0.2/0.1 mmHg lower ($p<0.001/0.02$) than BP averaged over the days 1 through to 7. There was a slight decreasing trend in both systolic and diastolic BP from the first day to the third measurement day (Table 2/Study I).

5.1.2 Association between home blood pressure and ambulatory blood pressure (I)

The correlation between home BP and ambulatory BP increased slightly with the cumulative number of home measurements. No major increase in the correlations occurred after day 4 (Table 3, Figure 1/Study I). The correlation between home BP and ambulatory BP was not significantly higher when the first day of the measurements was excluded from the mean of all measurements ($r=0.89/0.87$ vs. $r=0.89/0.87$ for systolic/diastolic home BP, $p=0.25/0.39$).

There were no significant differences in the correlations between systolic/diastolic ambulatory BP and the mean of first ($r=0.89/0.87$) or second home BP ($r=0.89/0.87$) measurements performed on each measurement occasion. No significant differences were found in the correlations between systolic/diastolic ambulatory BP and morning ($r=0.87/0.85$) or evening ($r=0.88/0.87$) home BP ($p=0.29/0.12$).

5.1.3 Association between home blood pressure and target organ damage (I)

The correlations between home BP and left ventricular mass index (LVMI) or urine microalbumin increased slightly with the cumulative number of home BP measurement days (Table 3, Figure 1/Study I). No major increase in the correlations occurred after day 4. The correlation between systolic/diastolic home BP and LVMI or urine microalbumin was not higher when the first day of the measurement was excluded (r=0.62/0.60 vs. r=0.62/0.60 for LVMI, p=0.26/0.10 and r=0.34/0.33 vs. 0.34/0.33, p=0.39/0.75 for urine microalbumin). The correlations between LVMI and the mean of the first (r=0.61/0.60) or the second home BP (r=0.62/0.59) measurements taken on each measurement occasion were equally strong (p=0.72/0.06). The same applied for urine microalbumin (r=0.33/0.33 vs. r=0.34/0.32, p=0.09/0.55). Both the systolic/diastolic morning home BP measurements (r=0.62/0.60) correlated slightly better than the evening home BP measurements (r=0.59/0.57) with LVMI (p=0.03/0.01). No significant differences were detected in the correlations between urine microalbumin and systolic/diastolic morning (r=0.34/0.33) or evening (r=0.33/0.31) home BP (p=0.70/0.40).

The results were similar in both hypertensive and normotensive populations (data not shown).

5.1.4 Association between home blood pressure and cardiovascular events (II)

Subjects who had suffered a CV event during the follow-up had significantly higher mean home BPs obtained during the morning of the first measurement day (1-morning, number of measurements=2), the first measurement day (1-day, n=4), the first two measurement days (2-day, n=8), days 2 to 7 (days 2-7, n=24), the whole week (1-week, n=28), the morning measurements (morning, n=14), the evening measurement (evening, n=14), the first measurements of each measurement occasion (first measurement, n=14), and the second measurements of each measurement occasion (second measurement, n=14) than those who had not (Table 2/Study II).

All BP variables (shown in Figures 1 and 2/Study II) were predictive of total CV risk ($p<0.001$ for all). Figure 1/Study II shows that the predictive value of home BP increased progressively with the cumulative number of measurements and the greatest predictive value was achieved by using the mean of all measurements (systolic/diastolic hazard ratio per 1 mmHg increase in BP, 1.021/1.034; systolic/diastolic 95% confidence interval [CI], 1.012-1.030/1.018-1.049). However, most of the increase in predictive value occurred during the first three days of measurement (RH, 1.017/1.028; 95% CI, 1.009-1.026/1.013-1.045). The predictive value also showed an increasing trend when individual measurement days were analysed separately, but this trend weakened after the third day of measurement, especially for diastolic BP (Figure 1/Study II).

The first measurement, second measurement, morning, evening, 7-day, and days 2-7 were all predictive of CV risk ($p<0.001$ for all, Figure 2/Study II). Table 3/Study II shows the likelihood ratio $\chi 2$ values when two BP indices were analysed simultaneously. When the first day of measurement was discarded, no additional benefit was achieved. The second measurement on each measurement occasion increased slightly the goodness-of-fit as compared with the model that included only the first measurements, but only with systolic BP. A model which compared the predictive values of the first measurement of each measurement occasion (14 measurements) with the measurements taken during the first three and a half days (14 measurements) was as well used in this study. There was no increase in the goodness-of-fit for systolic BP ($p=0.26$), but a slight increase for diastolic BP ($p=0.03$). Adding evening BP to the model which included morning BP did not result in a greater goodness-of-fit.

The correlations between home BP and target organ-damage, and the predictive values between home BP and cardiovascular events, in different measurement settings have been compared in Table 4.

Table 4. *The correlations/predictive values between home BP and target-organ damage/CV events in different measurement settings*

Measurement days	Target organ damage*			CV events†
	Ambulatory BP	LVMI	Microalbumin-uria	
Day 1	0.84/0.82	0.56/0.55	0.30/0.30	1.014/1.019
Days 1-3	0.88/0.85	0.59/0.58	0.33/0.32	1.017/1.028
Days 2-7	0.89/0.87	0.62/0.60	0.34/0.33	1.021/1.038
Days 1-7	0.89/0.87	0.62/0.60	0.34/0.33	1.021/1.034

*The Pearson correlation between systolic/diastolic home BP and target-organ damage

†Predictive values between systolic/diastolic home BP and CV events

BP, blood pressure; CV, cardiovascular

5.2 Factors affecting the difference between morning and evening home blood pressure (III)

5.2.1 Morning and evening home blood pressure level in study subjects with and without antihypertensive medication

In untreated hypertensive subjects, systolic home BP was lower in the morning than in the evening while no difference was detected in diastolic home BP (137.7/85.1 vs. 141.5/85.2 mmHg, $p<0.001/0.64$). In treated hypertensive subjects, the difference between systolic morning and evening BP was smaller (136.2 vs. 137.1 mmHg, $p=0.023$) and diastolic morning BP was even higher than evening BP (83.3 vs. 82.1 mmHg, $p<0.001$).

5.2.2 Associations between selected clinical variables and the morning-evening home blood pressure difference

In the univariate analysis, higher home BP and higher BMI were associated with relatively higher systolic and diastolic morning home BP compared with evening BP (Table 3/Study III). Higher age was associated with relatively higher diastolic morning home BP compared with evening BP, whereas no association was found between age and systolic morning and evening home BP difference. In addition, men, subjects with CV

disease, sleep apnea, excessive alcohol use, and subjects using antihypertensive medication had relatively higher morning BP compared with evening BP. Smokers had higher diastolic evening home BP compared with morning BP than non-smokers (Table 3/Study III), and they were also younger than non-smokers (53.4±7.2 vs. 57.4±8.7 years, $p<0.001$). Morning-evening home BP difference was not associated with the Cornell product [97-98] in the whole study population, in men or women (data not shown), either in treated or untreated subjects (data not shown).

5.2.3 Independent determinants of the morning-evening home blood pressure difference

In the multivariate linear regression analysis male gender, the use of antihypertensive medication, the presence of sleep apnea, a past history of CV disease and excessive use of alcohol were all independent determinants of elevated systolic and diastolic morning home BP compared with evening BP (Table 4/Study III). Smoking was an independent determinant of an elevated diastolic evening home BP compared with morning BP, and high BMI an independent determinant of an elevated diastolic morning home BP compared with evening BP (Table 4/Study III). The independent determinants affecting morning-evening home BP difference are presented in Table 5.

Table 5. *Independent determinants of morning-evening home blood pressure difference*

Determinant	Morning BP higher than evening BP systolic/diastolic (mmHg)
Male gender	0.21/1.91
Subjects using antihypertensive medication	1.03/2.05
Subjects with sleep apnea	0.38/1.83
Subjects with past history of CV disease	0.47/1.92
Subjects with excessive alcohol consumption	1.13/2.48

BP, blood pressure; CV, cardiovascular

5.3 Factors affecting the variability of home-measured blood pressure and heart rate (IV)

The mean values of the variability variables in home-measured BP and HR are presented in Table 1/Study IV. The distribution of home BP variability is presented in Figure 1/Study IV and home HR variability in Figure 2/Study IV.

5.3.1 Determinants of home blood pressure variability

Univariate associations of home blood pressure variability

Old age, high home BP, high BMI, use of antihypertensive medication, CV disease and diabetes were associated with greater systolic and diastolic morning minus evening, day-by-day and first minus second measurement of home BP variability (Table 2/Study IV). There were significant differences between alcohol usage groups in morning minus evening, day-by-day and first minus second measurement of home BP variability (Table 2/Study IV). Smoking and sleep apnea were not associated with any of the home BP variability variables.

Morning minus evening home blood pressure variability

Old age, past history of CV disease, diabetes and high systolic/diastolic home BP were independent determinants of both greater systolic and diastolic morning minus evening home BP variability (Table 3/Study IV). Female sex, low BMI and excessive use of alcohol were independent determinants of greater systolic morning minus evening home BP variability.

Day-by-day home blood pressure variability

Old age, high systolic/diastolic home BP and excessive use of alcohol were independent determinants of both greater systolic and diastolic home day-by-day BP variability (Table 3/Study IV).

The use of antihypertensive medication, high home HR, low BMI and being of the female sex were independent determinants of greater systolic day-by-day home BP variability. CV disease and smoking were independent determinants of greater diastolic day-by-day home BP variability. When day-by-day home BP variability was divided into morning and evening components, the associations were almost similar,

except for excessive use of alcohol, which was not associated with systolic morning day-by-day variability (data not shown).

The variability of first minus second home blood pressure measurement

Old age, female sex, high systolic/diastolic home BP and CV disease were independent determinants of both greater systolic and diastolic first minus second measurement of home BP variability. High home HR and excessive use of alcohol were independent determinants of systolic first minus second measurement of home BP variability, and high BMI and diabetes were independent determinants of diastolic first minus second measurement of home BP variability.

5.3.2 Determinants of home heart rate variability

Univariate associations of home heart rate variability

High home HR, young age, absence of antihypertensive medication and smoking were associated with greater morning minus evening, day-by-day and first minus second measurement of home HR variability (Table 2/Study IV). Sleep apnea was associated with lower morning minus evening and first minus second measurements of home HR variability. Moreover, high diastolic home BP was associated with greater morning minus evening and day-by-day home HR variability. There were significant differences between the alcohol usage groups in morning minus evening, day-by-day and first minus second measurement of home HR variability.

Morning minus evening home heart rate variability

A younger age-group, high home HR, absence of sleep apnea and moderate use of alcohol were independent determinants of greater morning minus evening home HR variability (Table 4/Study IV).

Day-by-day home heart rate variability

Being of a younger age-group, high home HR, high diastolic home BP and use of alcohol were independent determinants of greater day-by-day home HR variability (Table 4/Study IV). When day-by-day home HR variability was divided between the morning and evening components, the associations were almost similar, except for smoking and excessive use of alcohol, which were independent determinants of greater morning day-by-day variability (data not shown).

The variability of first minus second home heart rate measurement

Being of a younger age-group, female sex and high home HR were independent determinants of greater first minus second measurement of home HR variability (Table 4/Study IV).

5.3.3 Coefficient of variation

When the coefficient of variation was used as a measure of variability instead of SD, the results of the variability in home-measured day-by-day BP and HR were mainly similar (data not shown). Variances explained by the multivariate models were lower when the coefficient of variation was used instead of SD (data not shown).

A summary of the independent determinants of the home BP variability and home HR variability are presented in Table 6.

***Table 6**. Independent determinants of home blood pressure variability and home heart rate variability.*

	Independent determinants of higher home BP variability						
Variable	**Old age**	**High home BP**	**CV disease**	**Diabetes**	**Excessive use of alcohol**	**Female gender**
Morning-evening	X	X	X	X		
Day-by-day	X	X			X	
1st-2nd	X	X	X			X

	Independent determinants of higher home HR variability				
Variable	**Young age**	**High home HR**	**Moderate use of alcohol**	**Excessive use of alcohol**	**Female gender**
Morning-evening	X	X	X		
Day-by-day	X	X		X	
1st-2nd	X	X			X

BP, blood pressure; CV, cardiovascular; HR, heart rate
Only significant ($p<0.05$) determinants of both systolic and diastolic home BP /home HR variability included

5.4 Prognostic value of the variability in home-measured blood pressure and heart rate (V)

Baseline variability of home BP and HR in the study population with or without a CV event during the follow-up are reported in Table 3/Study V. Home BP variation was higher in subjects who had suffered a CV event than in healthy subjects. On the contrary, no difference was detected in home HR variability variables between the two groups.

5.4.1 Home blood pressure variability and home heart rate variability as predictors of cardiovascular events

In the unadjusted Cox regression models, all the home BP variability variables, but none of the home HR variability variables were predictive of CV events (Table 1s/Study V). After adjustments for other risk factors, both systolic and diastolic morning minus evening home BP variability and morning day-by-day home BP variability remained as independent predictors of CV events (Table 4/Study V). Diastolic day-by-day and first minus second measurement of home BP variability were equally predictive of CV events. In contrast, morning minus evening HR variability and morning day-by-day HR became predictors of CV events in the adjusted models. More specifically, morning-evening HR variability and morning day-by-day HR variability both became predictive of CV events after age was added as the only covariate in the models (for morning-evening HR variability RH, 1.08; 95% CI, 1.04-1.13; p=0.01, per 1 beat/min increase in HR variability, and for morning day-by-day HR variability RH, 1.11; 95% CI, 1.06-1.17; p=0.002, per 1 beat/min increase in HR variability).

In the subgroup analyses of strokes, only diastolic first minus second measurement of home BP variability was predictive of stroke events (RH, 1.13; 95% CI, 1.03-1.25; p=0.042, per 1 mmHg increase in BP variability) in the adjusted model. None of the home HR variability measurements predicted strokes (data not shown).

5.4.2 Home blood pressure variability and home heart rate variability as predictors of total mortality

In the unadjusted Cox regression models, all home BP variability variables, as well as morning minus evening and morning day-by-day variables of home HR variability predicted total mortality (Table 3/Study V).
In the adjusted models, all the other diastolic home BP variability variables, except diastolic evening day-by-day home BP variability, were predictive of all-cause mortality (Table 4/Study V). Systolic morning day-by-day home BP variability was the only systolic home BP variability predictor of all-cause mortality. Moreover, morning-evening and morning day-by-day home HR variability variables were predictive of all-cause mortality in the adjusted models.

5.4.3 The additive effect of home blood pressure variability and home heart rate variability as predictors of cardiovascular events

The cumulative risk between CV events and morning systolic/diastolic home BP variability, as well as the CV risk between home HR variability at different BP levels are presented in Figure 1/Study V. The cumulative risk between CV events and home HR variability at different HR levels was not clinically meaningful since home HR level itself was not associated with CV events (p=0.70).

When systolic/diastolic morning day-by-day home BP variability was adjusted for morning day-by-day home HR variability and for other CV risk covariates used in Table 4/Study V, systolic/diastolic morning home BP variability did not remain as an independent determinant of CV events. The same result was found when systolic morning minus evening home BP was adjusted for morning minus evening home HR variability and other CV risk covariates. When diastolic morning minus evening home BP variability was adjusted for morning minus evening HR variability and other CV risk covariates, diastolic morning minus evening home BP variability remained as an independent determinant (RH=1.08; 95% CI, 1.03-1.13, p=0.02 per 1 mmHg increase in BP variability).
When morning day-by-day home HR variability was adjusted for systolic/diastolic morning home BP variability and other CV risk

covariates, morning home HR variability remained as an independent determinant for CV events (RH=1.10; 95% CI, 1.04-1.16, p=0.009 per 1 beat/min increase in HR variability adjusted for systolic morning BP variability, and RH=1.08; 95% CI, 1.02-1.15, p=0.02 adjusted for diastolic morning BP variability). When morning minus evening home HR variability was adjusted for systolic/diastolic morning minus evening home BP variability and other CV risk covariates, it did not reach statistical significance.
The additive effect of diastolic morning home BP variability and morning home HR variability for CV risk at different home BP levels is presented in Figure 2/Study V.

5.4.4 Coefficient of variation

Using the coefficient of variation instead of SDs of day-by-day and morning/evening day-by-day home BP and home HR produced similar results, in both unadjusted and adjusted models (data not shown).

6 Discussion

6.1 Optimal schedule for home blood pressure monitoring (I and II)

6.1.1 Optimal schedule for home blood pressure measurement based on the correlation with target-organ damage and ambulatory blood pressure

Home BP decreased gradually to a near-plateau level as the individuals became accustomed to home BP measurements. This has been demonstrated in previous studies as well [40, 104-105].

The correlations of home BP with target-organ damage and ambulatory BP increased with the cumulative number of measurement days, although no major increase occurred after day 4. Maximal correlations were achieved when all 28 measurements were used. There was no change in the correlations when the measurements performed during the first day were discarded.

The associations of home BP with ambulatory BP and microalbuminuria were equally strong when home BP was measured in the morning and in the evening and small, clinically insignificant difference was detected for LVMI. These results suggest that there might not be any difference whether morning or evening measurements are used in the evaluation of CV risk. However, measuring both morning and evening home BP is important for assessing the 24-h efficacy of antihypertensive treatment [70-72].

The mean of the second home BP measurements on each measurement occasion was lower than the mean of the first measurements. This finding may suggest that individuals measuring home BP are more anxious during the first measurements and therefore, home BP level obtained in the second measurements better represents the true BP level. This finding emphasized the importance of rest before performing home BP measurements. The first measurements should not be discarded because

including both first and second measurements resulted in the highest correlations.

As home BP decreased, the association between home BP and ambulatory BP or target-organ damage increased. Therefore, the number of the measurements seems to be the most important factor in measuring home BP. Most of the decrease in home BP and increase in correlations occurred during the first 4 days of the measurements. The results were similar in both hypertensive and normotensive populations.

6.1.2 Optimal schedule for home blood pressure measurement based on future cardiovascular events

The predictive value of home BP increases progressively with the number of measurements, showing the highest predictive value with the average of all measurements performed during one week. However, a clear majority of this increase is achieved during the first three days of measurement. No additional benefit in predictive ability is achieved when the values obtained during the first day of measurement are discarded. Morning and evening BP are equally predictive of future CV events. Measurement of home BP twice, instead of once, on each measurement occasion offers a marginally better predictive value as it doubles the number of measurements, but only with systolic BP.

It has been previously demonstrated by the Ohasama group that the predictive value for stroke risk associated with home BP increases progressively within the range of 1–14 measurements performed during one week without any clear threshold [43]. This study, with 28 measurements performed during one week, also demonstrates that the predictive value of home BP increases progressively with the number of measurements, showing the highest predictive value with the average of all measurements performed during one week. However, a clear majority of this increase is achieved during the first three days of measurement and only minimal increase occurs after day 6. These data confirm previous cross-sectional findings demonstrating that the correlation between home BP and hypertensive target-organ damage increases slightly but steadily over a one-week home BP measurement period, and that only marginal increase occurs after the sixth day of measurement (Study I) [98, 106]. Measurement of home BP preferably for a period of seven days, or for at

least three days, is therefore needed to obtain a thorough image of a patient's true BP level.

The current guidelines recommend from one to three measurements on each occasion, although the two largest epidemiological studies have been performed with just one home BP measurement on each occasion [22, 49, 64, 69]. The recommendations of the European and American guidelines are mostly based on the evidence that regression to the mean during consecutive measurements on each occasion is frequently observed even after long-term monitoring [107]. However, the Japanese Society of Hypertension guidelines for self-monitoring of BP at home recommend at least one measurement on each occasion without denying that multiple measurements might be of value, but this recommendation is based mostly on pure speculation according to which it would be more convenient and result in better compliance [85]. In our study, the second measurement produced on average 3/1 mmHg lower BP values than the first measurement and it increased the predictive value of systolic BP. Furthermore, 14 measurements measured twice on seven occasions seem to provide additional predictive value over 14 measurements performed once on 14 occasions. The Finn-home study demonstrates that performing two measurements on each occasion does not result in poor compliance since the study subjects measured their BP on average 27 times out of the 28 possible. However, this was an epidemiological study without a doctor-patient relationship and self-reported BP readings. In real-life clinical practice, adherence to measurements might not be as good as those observed in our study. Although the raw number of measurements seems to be the most important factor in determining predictive value, home BP should be measured twice on each occasion because of a lower number of required measurement days, a slightly better predictive ability, and the regression to the mean effect.

Results from the Ohasama study and our study suggest that discarding the first day of measurements could not necessarily be applicable from the viewpoint of prognostic significance [108]. Due to the large overlap in the mean BP for days 1-7 and days 2-7, the significance of the first day is quite miniscule.

The differences in morning and evening home BP in the general population are quite small, under 2 mmHg [43, 104, 109]. This study and a previous study by the Ohasama group also demonstrate that morning and evening home BP seem to provide equally useful information for CV

risk [110]. However, antihypertensive treatment alters the difference between morning and evening BP, and morning hypertension might be a slightly better predictor of stroke risk among individuals using antihypertensive medication (Study III) [104, 110]. An analysis of such a kind was not performed in this study due to the small number of events among the treated hypertensives (n=63). Thorough morning home BP measurements and evening measurements can also be used effectively for assessing the duration of antihypertensive drug action in patients [70, 72]. Home measurements in the morning and in the evening are therefore recommended for obtaining a thorough image of the average BP and to evaluate the round-the-clock efficacy of antihypertensive medication.

6.1.3 Consensus for optimal schedule for home blood pressure measurement

Current European guidelines [49] recommend discarding home BP measurements made on the first day since higher and more unstable values are usually obtained during the first home BP measurements [104, 107-108]. This phenomenon has been shown in studies on selected hypertensive populations [62, 107], and it appears to be present also in the population as a whole [104, 108]. The plateau level that is reached in BP with an increasing number of home BP measurements, as the patient becomes acquainted with home measurement, could therefore best represent the subjects' "true" BP level.
Based on this thesis, the correlations of home BP with ambulatory BP (Study I) and target-organ damage (Study I) [98, 106], and the predictive power of home BP measurements on CV events (Study II), no additional benefit was attainable if the values obtained during the first day of the measurements were discarded, even when only 12 measurements were available. Discarding the home BP values of the initial day makes the measurement schedule more complex for the patient and the treating physician. Furthermore, the alerting reaction seen during the first days of the initial measurement week will most likely attenuate during the following week-long measurement sessions. Therefore, the first day of the measurements should be included in the measurement schedule.

In conclusion, based on this study, it can be recommended that home BP should be measured on at least 4 days and preferably on 7 days, with duplicate measurements in the morning and in the evening. The first and

second measurements on each measurement occasion should be included along with the values obtained during the first day of measurements.

6.2 Factors affecting the difference between morning and evening home blood pressure (III)

6.2.1 Quantitative differences between morning and evening home blood pressure

Evening home BP was higher than morning home BP (Study III, Table 1 and 2), which is in accordance with studies performed in Europe [39-42]. However, in Japanese studies, morning BP is consistently higher than evening BP [43-46] which could be attributed to the differences between Japanese and European studies. The Japanese guidelines recommend measuring evening home BP before going to bed [85], whereas in this study and in the other European studies, home BP was measured at a fixed time, usually a few hours before going to bed. Furthermore, it has been shown that the evening measurements in Japan are often performed after taking a hot bath, which lowers BP by vasodilatation [45, 111].

6.2.2 Morning and evening home blood pressure in treated and in untreated subjects

In untreated hypertensive subjects, systolic home BP was lower in the morning than in the evening while no difference was detected for diastolic home BP (Study III, Table 2). In treated hypertensive subjects, the difference between systolic morning and evening BP was smaller. Conversely, diastolic morning BP was even higher than evening BP.
When the study population was classified according to JNC-7 criteria, hypertensive subjects had higher systolic and diastolic morning BP compared with evening BP than prehypertensive or normotensive subjects. No significant difference was detected in the morning BP compared with evening BP between normotensive and prehypertensive groups.
The smaller difference between morning and evening home BPs in treated subjects, which was also observed in the Hypertension Optimal Treatment (HOT) study [112], is most likely explained by the fact that the study subjects were instructed to measure morning home BP before taking their

antihypertensive medication. Antihypertensive medication is usually taken once a day, typically in the morning [113]. The peak of the antihypertensive effect is seen in the evening which balances the difference between morning and evening BP. Home BP monitoring has been shown to provide a good alternative to ambulatory monitoring for obtaining a precise and unbiased evaluation of 24-h antihypertensive drug effect [70-72].

6.2.3 Qualitative differences between morning and evening home blood pressure

Male gender, excessive use of alcohol, use of antihypertensive medication, a past history of CV disease and sleep apnea were independent determinants of elevated morning home BP compared with evening BP.

Alcohol
Excessive use of alcohol was an independent determinant for an elevated morning BP compared with evening BP. Subjects using excessive amounts of alcohol had their morning BP at a higher level than non-alcohol and moderate alcohol users. In addition, subjects moderately taking alcohol had a lower BP level (morning and evening) than non-alcohol users. Despite this observation, no difference was detected in the morning-evening difference between moderate users and zero users. A small amount of alcohol seems therefore not to affect the difference between morning and evening home BP.
In general, alcohol intake causes BP to decrease during the first few hours, while thereafter increasing it, this resulting in a higher BP level [7]. The acute BP decrease (in the hours after exposure) is due to vasodilation and is followed by BP elevation (next day) which is caused by sympathetic nervous activity [7]. Since alcohol is usually consumed in the evenings, this results in a relatively lower evening BP and higher morning BP [7, 56]. The finding in this study is in accordance with previous Japanese studies in which regular alcohol drinking was an independent determinant of an elevated morning BP compared with evening BP [44-45].

Sleep apnea
Sleep apnea is a very common disease and its prevalence is 4% among men and 2% among women in middle-aged adults [114]. Epidemiological studies have also revealed that obstructive sleep apnea is a risk factor for

developing hypertension [115]. In our study, sleep apnea was independently associated with an elevated morning home BP compared with evening BP. This finding is most likely explained by the fact that apneic sleep elevates BP and results in an elevated morning home BP compared with evening BP [48]. A similar finding has been previously found in one study [116]. Since sleep apnea continues to be an important public health care issue, a high morning home BP compared with evening BP could be used to identify subjects suffering from it.

Past history of cardiovascular disease
A past history of CV disease was also independently associated with an elevated morning home BP compared with evening BP. In subjects with CV disease, impairment of cerebral autoregulation has been put forward as a cause for morning surge (elevated morning BP) [117]. Elevated morning home BP compared with evening BP was seen in subjects with CV disease. Nonetheless, LVH, estimated by using the Cornell product, was not associated with greater morning home BP compared with evening BP. This may imply that some factors other than cardiac-based target-organ damage (measured by ECG-LVH) are responsible for an elevated morning home BP compared with evening BP. However, providing a reason for this finding requires further study.

Gender
Male gender was an independent determinant of an elevated morning home BP compared with evening BP, which is in accordance with the findings in the Japanese Ohasama study [43]. Several potential differences between men and women, such as BP regulating hormones, may partly explain the elevated morning home BP compared with evening BP. In addition, lower morning home BP compared with evening BP in females also leaves room for examining the different types of stress load during the day in men and women [118], i.e. females may have more additional work with the family in the evening, which might elevate their evening BP. However, the precise physiological causes for this phenomenon remain unknown and warrant further study.

Smoking and body mass index
Non-smoking was an independent determinant of an elevated diastolic morning home BP compared with evening BP, although study subjects were instructed to avoid smoking for 1 h before performing the home BP measurements. In addition, smokers were younger than non-smokers.

Therefore, our study finding suggests that daytime smoking may elevate evening home BP. This elevation in BP is thought to be partly mediated through the stimulation of sympathetic nervous system consequently leading to an increased plasma norepinephrine and epinephrine levels [8]. The pressor effect of smoking caused by nicotine (stimulating release of norepinephrine) is transient and is over after 30 minutes [8]. On the other hand, smoking impairs nitric oxide dependent vasodilation by increasing oxidative stress and plasma asymmetric dimethyl arginine (nitric oxide synthase inhibitor) levels, leading to elevated BP [119]. High BMI (>30 kg/m^2) was also an independent determinant of an elevated diastolic morning home BP compared with evening BP. Our finding is in accordance with a study where overweight subjects were likely to have a reduced nocturnal fall in BP, which is seen in our study as an elevated diastolic morning BP [120].

6.2.4 Morning and evening home blood pressure measurements in clinical practice

This study suggests that both morning and evening home BP should be used to assess the mean BP load, especially in subjects using antihypertensive medication. Awareness of the patient's elevated morning home BP compared with evening BP enables physicians to evaluate the 24-h efficacy of antihypertensive treatment. In addition, these results provide physicians with better knowledge of the factors affecting the elevated morning home BP compared with evening BP and help them understand the underlying causes. Physicians could thus find the appropriate treatment (adjust antihypertensive medication or further examine probable sleep disorder), and recommend lifestyle adjustments (alcohol and CV disease prevention counseling) that will be effective for individual patients.

6.3 Factors affecting the variability of home-measured blood pressure and heart rate (IV)

This study assessed for the first time the factors affecting the variability of home BP and HR in a general population using ESH home measurement recommendations.

6.3.1 Determinants of home blood pressure variability

Age
Old age was independently associated with greater morning minus evening, day-by-day and first minus second measurement of home BP variability. This can be attributed to the increased arterial stiffness due to age-related changes in contents of the arterial vessel wall (elastin is replaced by collagen), which magnifies BP changes and, therefore, increases variability [121-122].

Diabetes
Moreover, diabetes was an independent determinant of greater morning minus evening home BP variability. Hyperglycemia also affects the arterial vessel wall proteins and leads to arterial stiffening and a higher home BP variability [123].

Home blood pressure level
In addition, elevated BP level remained as an independent determinant for greater morning minus evening, day-by-day and first minus second measurement of home BP variability, which can be attributed to the greater magnitude of BP variation at higher levels of BP.

Cardiovascular disease
CV disease was, as well, an independent determinant of greater morning minus evening and first minus second measurements of home BP variability. More specifically, CV disease was an independent determinant of greater first minus second measurement of home BP variability only in women, in older participants (aged 56 years or over) of both sexes and in participants using antihypertensive medication. The association between CV events and greater short-term and day-by-day BP variability has been found in prognostic studies as well [55, 60].

Alcohol consumption
Excessive use of alcohol was an independent determinant for greater systolic and diastolic day-by-day, and in addition, systolic morning minus evening and first minus second measurements of home BP variability. In the subgroup analyses, the association between the greater home BP variability and use of alcohol was especially seen in men, which might be due to higher consumption of alcohol in men. In Finland, the peak of the alcohol consumption is concentrated on the last days of the week (Friday

and Saturday), whereas on the other days, the consumption is lower [124]. Alcohol intake causes BP to decrease during the first few hours (due to vasodilatation) and, thereafter increases it (due to sympathetic nervous activation, resulting in a positive net effect [7]. Excessive use of alcohol could, therefore, increase home BP variability by increasing sympathetic activity [125-126] and by elevating BP [127]. This could be seen in the present study as a greater variability between measurement days and also between measurement occasions.

6.3.2 Determinants of home heart rate variability

Alcohol consumption
Excessive and moderate uses of alcohol were independent determinants of greater day-by-day home HR variability, whereas moderate use of alcohol was an independent determinant of greater morning minus evening home HR variability. More specifically, the use of alcohol was an independent determinant of greater morning minus evening home HR variability, only in younger participants (aged 55 years or less) and in women. Alcohol drinking leads to vasodilatation (for a few hours), and next day to an increased sympathetic activity (leading to elevated HR) [125-126]. This is seen in our study as a greater home HR variability between measurement days, especially in excessive users of alcohol. The same effect, which is seen in BP variation, is also present in HR variation. That is, alcohol consumption is concentrated unevenly between the weekdays (the peak in consumption is seen on Friday and Saturday) [124], which may contribute to greater home HR variability between measurement days in excessive users of alcohol. In moderate users (especially in women and younger participants), the effect of alcohol is rather seen in greater morning minus evening HR variability than in greater day-by-day variability.

Smoking
Study participants were instructed to avoid smoking for 1 h before performing the home BP and HR measurements. Despite this fact, in the univariate analysis, smoking was associated with greater morning minus evening, day-by-day and first minus second measurements of home HR variability, but in the multivariate models adjusted with home HR level, smoking was not an independent determinant. This might be partly because smoking elevates HR by stimulation of the sympathetic nervous system, leading to an increased plasma norepinephrine and epinephrine

levels [8], but does not increase the actual home HR variability. The pressor effect of smoking caused by nicotine (stimulating release of norepinephrine) might be also missed in BP monitoring since it is over by 30 minutes [8, 128]. On the other hand, smoking impairs nitric oxide dependent vasodilation by increasing oxidative stress and plasma asymmetric dimethyl arginine (nitric oxide synthase inhibitor) levels, leading to elevated HR [119].

Age
A younger age was, as well, an independent determinant of greater morning minus evening, day-by-day and first minus second measurements of home HR variability. Furthermore, in subgroup analyses, use of alcohol was an independent determinant of greater home HR variability only in younger participants (aged 55 years or less). This is obvious as younger people have more adaptable and effective baroreflex buffering, which is seen as an increased home HR variability between measurement days and measurement occasions [51].

6.3.3 The variability of home-measured blood pressure and heart rate in clinical practice

Old age, diabetes, CV disease and excessive use of alcohol may increase home BP variability, and on the contrary, a younger age and use of alcohol may increase home HR variability. As home BP variability and home HR variability have prognostic significance, it is important for physicians to understand the underlying causes of home-measured BP and HR variability. In this way, they can focus on alcohol, diabetes and CV disease-prevention counselling for their high-risk patients.

6.4 Prognostic value of the variability in home-measured blood pressure and heart rate (V)

The value of BP and HR monitoring is not only limited to their absolute level, since high variability of BP and HR in ambulatory recordings have been associated with target-organ damage and CV events [51-55, 57, 59]. This study addressed for the first time the prognostic implications of the variability in home-measured BP and HR in European population and has compared the prognostic value of the variability in home-measured BP

and HR in different measurement settings (morning-evening, day-by-day, morning/evening day-by-day and first minus second measurement of variability).

6.4.1 Home blood pressure variability as a predictor of cardiovascular events

The association between higher home BP variability and CV events may partly reflect underlying disease states. In the cross-sectional study of the variability in home-measured BP and HR (Study IV), diabetes and a past history of CV disease were independent determinants of higher home BP variability. Aging and diabetes hasten the arterial stiffening process leading to changes in contents of the arterial vessel wall (elastin is replaced by collagen) [121-122]. This can magnify BP changes and increase BP variability.
Morning day-by-day home BP variability predicted CV events whereas evening day-by-day BP variability did not. The prevalence of CV complications has been shown to be higher in the morning than at other times of the day [117, 129]. This has been linked to the activation of the sympathetic nervous system [130] and to an increase in platelet aggregability [129]. Higher morning day-by-day home BP variability may therefore reflect greater hemodynamical instability and exposure to CV events. Higher morning-evening home BP variability also predicted CV events which supports the theory of greater hemodynamical instability in subjects at risk of CV events. In the Japanese Ohasama study day-by-day home BP variability (measured in the morning) was predictive of CV mortality which is in accordance with our study [60].
However, in the Ohasama study day-by-day home BP variability was also predictive of stroke mortality, whereas in our study home day-by-day BP variability did not predict strokes. This may be partly attributed to the differences between study populations, and, in addition, to the smaller number of strokes in our study.

Diastolic first minus second measurement of home BP variability predicted CV events (Table 4). This variability variable can be generally considered to indicate better short-time variability than the other home variability variables, since there is only a gap of a few minutes between the measurements. Therefore, greater first minus second measurement of home BP variability indicates the reactivity of an individual, seen as a

high variation of BP between the measurement occasions. The link between the reactivity and high variation between measurement occasions might be explained by the autonomic nervous system activation and arterial baroreflex since short-term alteration in BP is regulated primarily by these two factors [117].

6.4.2 Home heart rate variability as a predictor of cardiovascular events

Morning day-by-day home HR variability predicted CV events in the fully adjusted models, whereas home evening day-by-day HR variability did not (Table 4). Moreover, the variability of morning home HR and morning-evening home HR were predictive of CV events in the fully adjusted models but not in unadjusted models (Tables 3 and 4). Age was the primary covariate to explain this. As shown in our previous study (Study IV), being of a younger age was an independent determinant of greater home HR variability. Including age as a covariate in the analyses, indicates that especially older subjects with high HR variation are at the greatest risk of a CV event, since older people generally are more likely to have an underlying CV disease, which could lead to hemodynamic instability seen as fluctuations in HR.

In addition, morning home HR variability predicted CV events independently of morning home BP variability. However, home HR level was not predictive of CV events. This was a surprising finding since in the Japanese Ohasama study home HR predicted CV mortality in general population [131]. The association between higher morning day-by-day HR variability and CV events may reflect as well a greater hemodynamical instability due to impairment in cerebral autoregulation [117]. Hemodynamical instability can be as well the underlying cause in the association between greater variability of morning-evening home HR and CV events. In the Japanese Ohasama-study where home measurements were performed once every morning, day-by-day home HR variability was, as in our study, predictive of CV mortality although in the Ohasama study morning and evening HR variability was not separately examined [60]. None of the home HR variability measurements were predictive of stroke events in our study. The similar finding was also made in the Ohasama study where home HR variability did not predict stroke mortality.

6.4.3 Prognostic value of the variability in home-measured blood pressure and heart rate in clinical practice

This prospective study provides first evidence that higher morning-evening and morning day-by-day home BP and HR variability predicts CV events. Moreover, morning day-by-day home HR variability predicted CV events independently of morning day-by-day home BP variability.
Hypertensive subjects with increased variability of BP and HR should therefore be identified as high-risk patients. In addition to measurement of home BP and HR levels, we should encourage physicians to use the variability of home BP and HR when assessing the CV risk of a hypertensive patient.

6.5 Prognostic value of morning and evening difference in home blood pressure and home heart rate

Greater difference between morning and evening home HR was predictive of CV events in the multivariate model, whereas such an association between morning and evening home BP was not found. This might be explained by the fact that the average BP level itself, rather than the relatively higher morning BP compared with evening BP, is the most important factor in the development of a CV event.
Instead, greater morning home HR compared with evening HR was an independent predictor of CV events in the multivariate model. This might be due to impaired baroreflex buffering [51] leading to higher morning HR in subjects at risk of a CV disease.

6.6 Benefits of home blood pressure and home heart rate monitoring

As the home measurements of BP and HR provide a reliable method for assessing the true BP and HR level of an individual, they provide also an enormous amount of data of the BP and HR level at different time-points throughout the day and between days.
When performed according to guidelines, measurement of BP and HR at home provides a reliable tool for physicians to assess an individual's

health status. Home BP and home HR level combined with the information of morning and evening home BP, as well as with the variability of home-measured BP and HR can provide valuable information for physicians working in clinical practice.

6.7 Limitations of the current international guidelines of home blood pressure monitoring

Although the current home BP monitoring guidelines provide a good basis to perform reliable home BP measurements, they are still far from excellent. As home BP monitoring can provide additional information, beyond the basic BP level, such as the value of different measurement settings and the variability of home BP and HR, the current guidelines do not answer to any of these questions. Until now, the reason for this has been the lack of knowledge concerning factors affecting morning and evening home BP difference, and factors affecting the difference of home BP variability variables, as well as the prognostic value of home BP variability.

6.8 Future applications of home blood pressure monitoring and its economical benefits

In this thesis, the optimal schedule for home BP monitoring was determined. Based on the data of target-organ damage and CV outcome home BP measurements should be performed preferably for a period of 7 days, but at least on three days, including morning and evening measurements (for reliable assessment of antihypertensive drug action).
The most important goal in the near future is to get the data gathered from home measurements to be applied effectively in clinical practice. In addition to the conventional home BP and home HR level, the morning and evening measurements, as well as, the variability of home measured BP and HR should be taken into account in clinical practise.
Computer-aided technologies could be used to collect and interpret data from measurements more efficiently. This includes, collecting and gathering data from home-measurements into repositories so as to be easily applicable by physicians.

Computer-aided technology can provide a great help in home BP monitoring and data acquiring. In the future, the data gathered from

individual home BP monitors can easily be delivered to physicians by using e.g. wireless networks. All the technology needed is already available, but the current problem is its integration into the practical solutions. Based on the home measurements, and other health examination data, automated computerized models could calculate the CV risk for an individual. However, to perform reliable CV risk calculations more studies are needed to model the overall CV risk. This information achieved from the future studies could be applied to build a universal CV risk model to be used by physicians in primary health care.

Home BP monitors with embedded wireless technology and integration into the physicians' database also makes enormous savings by offering an easy and reliable way of delivering home BP data from patient to physician and by providing a smooth access to home BP monitoring data history. This saves both the time of the patient and the physician and further improves the measurement compliance of the patient.

6.9 Unresolved issues in home-measured blood pressure and heart rate measurements

Although a lot of effort has already gone into making home BP monitoring more reliable and effective, there are still some tasks to be undertaken. The main objective is to build a unified model for home BP monitoring to be used in primary health care units and in the home. This includes not only the utilization of home BP and home HR level itself, but also the utilization of information gathered from morning and evening measurements and the variability measurements of home BP and home HR. Combining this home measurement data with other health information of the individual makes it possible to get a more thorough ‘image’ of the individual’s current health status.
As important as is the optimal utilization of home BP monitoring data, an accurately performed home BP/HR monitoring is at least of the same importance. There are already validation protocols available for home monitors [36], which set the minimum standard for home BP monitors. The problem with the current validation protocol is that the protocol takes into account validation only at the population level but does not make any validation at the individual level [38]. This means that with the current validation protocol a home BP monitor may be more accurate for some individuals than for others. At the moment, the individual consumer or a

health care professional has to count on the current protocol recommendations when choosing a home BP monitor.

6.10 Study limitations

6.10.1 Study I

The strength of the study is that it is based on clinical data instead of on statistical models in trying to define the best schedule for home BP measurements. Despite the clinical approach in trying to define the best schedule for home BP measurement, this study is still lacking the prognostic approach. A larger population-based follow-up study to assess the optimal schedule for home BP measurement is, therefore, needed.

6.10.2 Study II

Participants measured their BP under relatively controlled conditions, and received individual guidance on how to perform the measurements correctly. However, it is still possible that measurement procedure could have affected BP level. No information was available about the compliance of home BP measurements which could have given a more thorough image of the validity of the measurements made.

6.10.3 Study III

Because of the cross-sectional nature of this study, no cause – effect relationships can be drawn from our findings. In addition, the timing of taking antihypertensive medication, smoking or the use of alcohol was not controlled. Either we did not have data available about the history of hypertension, nor the history of how long the study-subjects had been using antihypertensive medication. Having this information available could have given a more thorough view of the effects of these determinants on an elevated morning home BP compared with evening BP.

6.10.4 Study IV

Because of the cross-sectional nature of this study, no cause–effect relationships can be drawn from our findings. The prognostic values of

home BP variability and HR variability remain to be determined in future studies.

6.10.5 Study V

Although the home BP and HR measurements were carefully assessed the study results must be interpreted with caution. The interview data and laboratory measurements were gathered at the baseline of the study, and therefore the possible changes in the persons' health status were not updated during the follow-up. Participants measured their BP and HR under relatively controlled conditions, and received individual guidance on how to perform the measurements correctly. However, it is still possible that measurement procedure could have affected BP variability. Even though this study assessed the prognostic value of the variability in home-measured BP and HR based on the CV outcome, additional research is warranted for examining whether CV prognosis can be improved by making lifestyle adjustments (e.g. reducing alcohol consumption and giving CV disease prevention counselling). This remains to be assessed in future studies.

7 Conclusions

This thesis was set out to provide insight into building an optimal measurement schedule for home BP monitoring, and to evaluate how to increase the prognostic value of home measurements by using variability parameters of home BP and HR measured over several days.

Based on the risk for target-organ damage (increased left ventricular mass and microalbuminuria) and future cardiovascular events, the measurement accuracy increased progressively with a cumulative number of measurements and the greatest value was achieved by using the mean of all measurements. Most of the increase occurred during the first 3 days of measurement. In contrast to what the European guidelines (2008) suggest, the measurements performed during the first day should not be discarded, as it makes the measurement schedule more complex for the patient and the treating physician. Currently, a great deal of conflict exists in the recommended home BP schedules in various international guidelines, and no agreement on this matter has yet been reached. Therefore, the novel information of this thesis could be used to prepare a unified international guideline for home BP measurements.

In addition, the measurement of home BP and home HR over 7 days can provide additional information since the variability of home BP and home HR has predicted future CV events.
In the general population, evening home BP was higher than morning home BP. In untreated hypertensive subjects, systolic home BP was lower in the morning than in the evening, while no difference was detected for diastolic home BP. In treated hypertensive subjects, the difference between systolic morning and evening BP was smaller. Conversely, diastolic morning BP was even higher than evening BP. Male gender, excessive use of alcohol, use of antihypertensive medication, past history of CV disease and sleep apnea were independent determinants of elevated systolic and diastolic morning home BP compared with evening BP. Having a knowledge of the underlying causes affecting morning and evening home BP difference in patients enables physicians to make possible medication and lifestyle adjustments. Physicians could find the appropriate treatment (adjust antihypertensive medication or further examine probable sleep disorder), and recommend lifestyle adjustments

(alcohol and CV disease prevention counselling) that will be effective for individual patients.

Old age, diabetes, CV disease and excessive use of alcohol were independently associated with increased home BP variability. Young age and use of alcohol were independently associated with increased home HR variability. As especially the variability of morning and morning-evening home BP and home HR are both independently associated with future CV events, it is important for physicians to understand the underlying causes of the variability in home-measured BP and HR. In this way, they can focus on alcohol, diabetes and CV disease prevention counselling for their patients.

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